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Horizon Scanning Centre

New and emerging health technologies for inherited retinal diseases

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EXECUTIVE SUMMARY

This review sought to identify new and emerging health technologies that aim to slow or stop disease progression and/or reverse sight loss in people with inherited retinal diseases.

Inherited retinal diseases are now the most common cause of blindness certification in England and Wales in working age adults and the second commonest in childhood. Currently, there is no cure or specific treatment. Management of these conditions revolves around early diagnosis, specialised genetic counselling, treatment of accompanying genetic conditions as well as visual rehabilitation, support and training (e.g. to use visual aids).

Searching of technology databases, bibliographic databases, clinical trial registries and other online sources was combined with company contacting and consultation with clinical experts, to identify relevant new and emerging health technologies.

Clinical experts and two patient focus groups (facilitated by the charity Fight for Sight) were asked to review the identified technologies and provide comment on innovation, potential for future impact (on patient outcomes, NHS systems and resources), current use, and any potential barriers to adoption. The patient focus groups provided valuable insights into the technologies presented from potential users perspective.

In total, forty new and emerging technologies were identified and included in the report: nine gene therapies; ten medical technologies; five pharmacological technologies; five regenerative and cell therapies; eleven very early developments (typically phase I or pre-clinical development stages). The vast majority of these technologies are subject to ongoing or anticipated clinical trials; very few treatments are already available in clinical practice to a limited number of patients.

Clinical expert and patient opinion indicates that the technologies likely to have the most impact in the future are gene therapies and regenerative and cell therapies. Some technologies are more applicable to earlier stages of disease such as gene therapy, while others are more applicable to advanced stages such as artificial vision and stem cell therapy. According to clinical experts, these treatments are not mutually exclusive and may be complementary, potentially used either together or sequentially.

Clinical experts commented that although this is time of great innovation for developing potential treatments for inherited retinal diseases, most of the health technologies identified in this review are still at an early stage of development. Further well designed trials and data on efficacy, applicability, and costs of the technologies as well as the long term impacts for various conditions are required, before these can be considered for adoption into clinical practice.

ACKNOWLEDGEMENTS

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The NIHR Horizon Scanning Centre also wishes to thank Carol Bewick (Director of Policy and Communications, Fight for Sight) and the charity's patient focus groups, who provided a valuable contribution to the review.

Statement of conflicts of interest
Professor Moore is Chairman of the data safety and management committee for the Oxford Biomedica gene therapy trials and is a consultant to Sanofi. He is also an Advisor to QLT, in their current trial of oral retinoids for retinal dystrophies. For this reason Professor Moore did not provide comments on these technologies.

1. INTRODUCTION

This review arose from the findings of the Sight Loss and Vision Priority Setting Partnership (PSP) facilitated by the James Lind Alliance and published in October 2013. This PSP highlighted unanswered questions about the treatment of sight loss due to inherited retinal diseases that patients, carers and eye health professionals wished to see addressed. This work led to and informed this review, which has been undertaken in close collaboration with the charity Fight for Sight, who were a member of the PSP Steering Group and helped develop the protocol for this review.

1.1 AIM AND OBJECTIVES

The review sought to identify new and emerging health technologies that aim to slow or stop disease progression and/or reverse sight loss in people with inherited retinal diseases.

The purpose of the review is to provide early intelligence to healthcare policy makers, commissioners, clinicians, patient groups and other interested parties about relevant health technologies in development.

1.2 CLINICAL NEED AND BURDEN OF DISEASE

Inherited retinal diseases (or hereditary retinal dystrophies) are a rare and diverse group of disorders that affect the retina and can result in severe visual impairment. The genetic causes for many of these disorders are currently unknown. There are over 100 inherited retinal diseases and severity varies.

Inherited retinal diseases are now the most common cause of blindness certification in England and Wales in working age adults and the second commonest in childhood[1]. This has significant implications for NHS resource allocation and research funding, as well as societal impacts including economic, psychological and emotional.

The internal structures of the human eye are shown in Appendix 1 for reference and background information on specific conditions referred to in this report can be found in Appendix 2.

1.3 CURRENT CLINICAL PRACTICE

There is no cure for inherited retinal diseases and the prognosis for patients can be poor. Management revolves around early diagnosis, specialised genetic counselling, treatment of accompanying genetic conditions as well as visual rehabilitation, support and training (e.g. to use visual aids).

Diagnosis

Diagnosis is difficult because conditions may present in similar ways and can look the same on examination and visual testing. For example, cone-rod dystrophy affects the macula (central region of the retina) in the same way as Stargardt disease, and sometimes it is not clear upon examination whether a young child has retinitis pigmentosa or a form of Leber's congenital amaurosis[2].

Diagnosis is made on clinical examination and subjective testing (e.g. colour vision tests or dark adaptometry). Additional testing is almost always needed, including electrophysiological testing such as electroretinograms (records action potential produced by the retina in response to light) and electrooculograms (measures standing potential between the electrically positive cornea and the electrically negative back of the eye), and detailed retinal imaging, including colour fundus photography, fluorescein angiography, autofluorescence imaging and optical coherence tomography. Increasingly more advanced retinal imaging such as adaptive optics imaging will be valuable. These more objective tests are important given the genetic implications of diagnosis, and help to differentiate between the vast array of inherited retinal diseases[3].

Another means of diagnosis is through a genetic test. Researchers in the UK have developed a new test that can analyse more than 100 genes in parallel, compared to fewer than 10 that current tests can scan. According to the researchers, the testing service will allow clinical experts to diagnose conditions such as isolated progressive retinal degeneration, Leber congenital amaurosis, and achromatopsia, as well as the two most common causes of syndromic blindness Usher and Bardet-Biedl syndromes[4].

Treatments

Treatment options for these conditions are limited and tend to be focused around optometric visual rehabilitation where possible including use of low vision aids, orientation and mobility training. It has been shown that taking active steps to train people in this way helps them maintain some degree of independence.

Some hospital eye clinics now have eye clinic liaison officers (ECLOs) who work with the medical teams to provide support (both practical and emotional) to patients diagnosed with an eye condition. Their role is to help patients better understand their diagnosis and most importantly help them maintain their independence. ECLOs should be able to provide up to date information about local and national resources and act as a patient advocate if needed.

Currently, the availability of highly specialised multidisciplinary services required to manage these conditions varies throughout the UK, with some areas having no access at all.

2. METHODS

2.1 SEARCH STRATEGY

We sought to identify new and emerging health technologies that aim to slow or stop progression and/or reverse sight loss in people with inherited retinal diseases by systematically searching a range of online and in-house sources of intelligence including:

- Technology databases e.g. NIHR HSC, Pharmaprojects, Adis Insight and international agencies such as ECRI and EuroScan.
- Bibliographic databases e.g. Medline and Embase.
- Research in progress e.g. ClinicalTrials.gov and Current Controlled Trials.
- Relevant conference reports and abstracts (December 2011 to December 2013).
- Review articles and commentaries in relevant specialist journals (December 2011 to December 2013).

- Websites and publications of key relevant organisations.

These were supplemented by a general information search via Google to access medical media reports, review articles and industry press releases. Searching took place from November 2013 to January 2014. A full list of identification sources and search terms used are provided in Appendix 3.

Ten clinical experts were identified and contacted to ask whether they could act as advisors. Four agreed to give their views on the technologies identified. They were also asked to provide information on new and emerging technologies known to them.

2.2 INCLUSION CRITERIA

A review protocol was developed and agreed with Fight for Sight. Searches were targeted towards technologies meeting the following criteria:

Technology type
Technologies that aim to slow or stop progression and/or reverse sight loss in inherited retinal diseases (pharmaceuticals, advanced [regenerative or cellular] therapies, and devices NOT diagnostic/prognostic tests).

Timeframe
Pharmaceuticals and therapies were included if there was a clinical trial with a relevant patient group and clinically relevant patient outcomes, typically phase II and phase III clinical trials (see Appendix 4 for an explanation of clinical trial phases).

Medical technologies were included if they were:
- 'emerging' – expected to be CE marked[a] (where appropriate) or launched within the UK within around two years.
- 'new' – CE marked (where appropriate) and usually only available for clinical use for less than one year. Generally in the launch or early post-marketing stages.
- 'new and poorly adopted' – this may include, for example, technologies that are within two years of launch and poorly diffused (available in less than 10% of NHS hospitals).

2.3 CONTACTING DEVELOPERS

Fifteen technologies were identified that required further investigation. The relevant developers and companies were contacted for information such as the phase of development and estimated timeframes for launch (availability for clinical use) in the UK. Non-responders were contacted a further two times. Of the 15 developers, only three responded to our request for additional information.

In many cases limited information was available and/or provided. Technologies no longer in development were excluded. Those presented are either confirmed to be in active development or have no up to date information available.

[a] CE marking indicates a product's compliance with EU legislation and therefore may be sold and distributed.

2.4 CLINICAL EXPERT AND PATIENT CONSULTATION

The four clinical experts were invited to comment on the potential significance of the list of technologies identified. In particular, opinion and comment were sought on the following: innovativeness; potential for impact on patient outcomes and NHS systems/resources; availability and use in the NHS; and potential barriers to adoption.

Comments on patient impact were also sought from patient focus groups set up and led by Carol Bewick, Fight for Sight. The two groups were held in March 2014 and included people with first-hand experience of inherited retinal conditions. The participant's condition and amount of sight loss varied.

Clinical and patient comments and opinions are incorporated into the results section of this report.

3. RESULTS

We identified a total of 40 innovative new and emerging technologies that met the inclusion criteria (Table 1). A detailed list of the technologies grouped according to the technology type can be found in Appendix 5. The tables include comments from the clinical experts and patient focus groups.

Table 1: Number of technologies identified according to type

Table	Type of technology	Total number
1	Gene therapy	9
2	Medical technologies	10
3	Pharmacological technologies (drugs)	5
4	Regenerative and cell therapies	5
5	Very early technologies (e.g. phase 1 and pre-clinical)	11

The development status (e.g. clinical trial phase) of each technology is provided in Appendix 5 if it was known or if it could be estimated. Most of the technologies are still in early phases of development (e.g. phase I/II) and depending on the outcome of the clinical trials will not be available for clinical use for several years. Some technologies identified are very early developments (e.g. phase I or pre-clinical), but have been included to provide a complete picture of developments on the horizon (Appendix 5 Table 5).

Many of the technologies are invasive treatments such as subretinal injections, implants and associated procedures (often involving complex surgery). There are risks generally associated with these treatments such as infection, damage to local structures and inflammation, all of which have the potential to worsen any remaining vision. Only one of the medical technologies, the Smart Glasses (number 18), is more 'assistive' and non-invasive.

4. OVERVIEW OF FINDINGS

Currently, there is no cure or specific treatment for inherited retinal diseases. Different research groups are working on correcting the underlying problem, regenerating damaged retinal cells, preventing further deterioration, providing artificial methods of sensing light, or improving assistive technologies.

The following technology overview provides some information on the technology/treatment groups (e.g. methods of delivery and potential side effects) and covers developments highlighted by clinical experts and the patient focus groups as being of interest in terms of technological innovation, and clinical and/or patient impact. A full list and technology-specific comments can be found in Appendix 5.

4.1 GENE THERAPY

Gene therapy (or gene replacement therapy) is designed to replace the faulty gene within the affected retinal cells. If this approach is successful, the cells will work correctly and the damage either stopped or reversed. This method relies on the gene causing the problem being known.

A carrier called a vector is genetically engineered to deliver the new gene. Typically viruses are used as vectors, but these viruses are modified so they cannot cause disease when used in people. Adenoviruses (or adeno-associated virus - AVV) and lentiviral vectors (version of equine infectious anaemia virus) are examples. A vector can be delivered via subretinal injection using a very fine needle. A patient's retina is first detached and then the virus is injected underneath. If the treatment is successful, the new gene delivered by the vector will make a functioning protein[5].

According to experts, clinical trials have reported some adverse effects using subretinal injections such as retinal detachments (macular and fovea), inflammation, structural changes (e.g. reduced foveal thickness) and some degree of photoreceptor disruption.

We identified nine gene therapy clinical trials covering five conditions: choroideremia, Leber's congenital amaurosis, retinitis pigmentosa MERTK mutation, retinitis pigmentosa associated with Usher syndrome type 1B, and Stargardt macular degeneration (Appendix 5 Table 1). The most advanced technology is in a phase III randomised controlled trial for Leber's congenital amaurosis (number 2). Expert comment indicates that this gene replacement therapy for patients with RPE65 deficiency has been shown to improve retinal function in some recipients, though the improvement in visual acuity is limited and it may not slow degeneration. The researchers have reported that younger patients benefit more from the treatment. This phase III trial may give useful information about the magnitude and the duration of any treatment effect.

An expert has indicated that further gene therapy trials are planned in one to three years time for conditions such as achromatopsia (CNGA3 and CNGB3-associated achromatopsia).

Gene therapy has the potential to slow and reverse retinal degeneration. It appears to be most effective in treating conditions before the degenerative process has resulted in extensive retinal cell loss. Current trials are at early stages and longer term follow up

(two to four years) will be needed to provide information on the effectiveness of the technology. An expert commented that if the current trials show benefits in terms of slowing retinal degeneration, a further randomised trial will be needed. Then an evaluation of whether the treatment is cost effective and has a significant effect on quality of life will be required, before it can be available for clinical use within the NHS.

4.2 MEDICAL TECHNOLOGIES

We identified 10 medical technologies (Appendix 5 Table 2). Most of these are implants that sit either on the retinal surface (epiretinal) or underneath the retina (subretinal), with some using an external camera on a spectacle frame linked to the implant to enable vision, whilst others incorporate light sensitive photodiodes.

Two technologies are CE marked and available for clinical use in the UK: the ARGUS II Retinal Prosthesis System and the Alpha IMS. The ARGUS II (number 11) is an implant designed to sit on the surface of the retina and stimulate remaining healthy cells of the retina. The implant receives information from a patient-worn video processing unit, which in turn receives signals from a miniature video camera housed in a pair of glasses. By learning how to interpret these signals, patients may potentially be able to continue using visual cues to guide their activities and maintain independent living for longer. The Alpha IMS implant (number 10) is designed to restore moderate sight in people blinded due to retinitis pigmentosa. The system replaces the function of the retina, capturing light onto a chip placed under the retina and stimulating the optic nerve based on what the chip sees. The implant does not use an external camera, so looking around is done naturally with the eyes rather than the head. Alpha-IMS delivers higher visual acuity, but smaller visual field (20/546, 15° visual field) than that of the Argus II (20/1262, 20° visual field)[6]. Therefore, Alpha-IMS's photodiode design may provide more focused central vision, while the Argus II provides broader, but less focused vision with its external camera and 60-electrode arrays[6].

Experts and the patient focus groups commented that it is difficult to know if the Stanford Implant Photovoltaic Retinal Prosthesis (number 19) will work without further research and the publication of results. Some doubts were expressed over whether this technology (i.e. wearing the 'gaming' style goggles) would be practical and acceptable, and therefore used by people in a public setting.

The patient focus groups commented that the appearance of technologies was important to younger people in particular, as wearing something seen as 'uncool' would be rejected by children and young adults. It was suggested that appearance should be part of any design from the start. One woman said that even carrying a white stick had been a 'barrier to cross' as it made her feel noticeably different from other people. The patient focus groups suggested that even where a technology is effective, if people do not wish to wear the new device because of how it looks, it will never be fully adopted.

Clinical experts commented that most of the devices are for patients with advanced and end stage disease; patients with retinal dystrophies who have lost the majority of their photoreceptors and have minimal vision. The idea behind these devices is that the nerve fibres of the retina are still intact in these patients and can be stimulated directly to give some form of vision. Patients will need training and support to help them to use the information transmitted to the visual cortex. These devices are not suitable for patients with infantile onset retinal dystrophies who have never had sight.

In addition, there are currently some unanswered questions to such devices, including long term biocompatibility (e.g. conjunctival erosion, retinal detachments, increased intraocular pressure and decreased retinal perfusion) and the long term effects of chronic nerve fibre stimulation[5].

4.3 PHARMACOLOGICAL TECHNOLOGIES

We identified five developments covering three conditions (retinitis pigmentosa, Leber's congenital amaurosis and Stargardt disease). Most are in early phase I/II clinical development (Appendix 5 Table 3).

Rescula (isopropyl unoprostone) eye drops (number 23) is in phase III development. This is currently used topically to treat glaucoma and has been reported to have neuroprotective effects on retinal neurons for the treatment of retinitis pigmentosa. An expert commented that trials of neuroprotective agents are difficult to do because large numbers of participants and long term follow up are needed.

Fenretinide (number 21) is an oral inhibitor of vitamin A delivery to the retinal pigment epithelium (RPE), the pigmented layer of the retina. It is thought to prevent the accumulation of toxins in the outer retina that may be responsible for loss of vision. Expert opinion suggests it may be worthy of investigation in Stargardt disease.

Most of the pharmaceuticals identified are in early phases of development and therefore it is difficult to estimate when they might become available for clinical use. There is little information currently on the potential side effects. Results of ongoing clinical trials are awaited.

4.4 REGENERATIVE AND CELL THERAPIES

Stem cells are able to divide and form many other cell types and have the potential to replace damaged or missing retinal cells. The field of stem cell-based therapy has potential for the treatment of inherited retinal diseases. Studies suggest that stem cells have the capacity to regenerate lost photoreceptors and retinal neurons and improve vision. Relevant stem cells include retinal progenitor cells (RPC), embryonic stem cells (ESC), induced pluripotent stem (iPS) cells, mesenchymal stem cells (MSC) and very small embryonic-like (VSEL) stem cells[7]. The techniques used are still relatively new, but their applications and benefits may be broad in the future. According to clinical experts, stem cell therapies are generally considered safe. However, a person's immune system may recognise the transplanted cells as foreign and this can trigger an immune reaction that results in rejection of the new cells.

We identified five technologies in development for conditions such as retinitis pigmentosa, choroideremia, Stargardt disease and Usher syndrome (Appendix 5 Table 4).

The clinical experts commented that an issue with the current trial using human embryonic stem cell (hESC)-derived retinal pigment epithelium (RPE) cells (number 26), is that the majority of patients with Stargardt disease who could benefit from stem cell therapy are likely to need replacement of both RPE cells and photoreceptors, and

this technology only replaces RPE cells. Experts were doubtful that this will be clinically effective in patients with Stargardt disease.

NT-501 ciliary neurotrophic factor implant (number 25), an encapsulated cell technology, was of most interest to the patient focus groups and growth factors in general were highlighted by the clinical experts as an area of innovation. Growth factors are substances that promote the health and function of cells and tissues in the body. They are made by the body to enable it to sustain and repair itself, and have important roles in cell survival. Ciliary Neurotrophic Factor has a specific role in nourishing nerve cells and has been shown to be successful in slowing retinal degeneration in animal models of retinitis pigmentosa[8]. Human clinical trials are also being undertaken.

It is difficult to estimate when research might be translated into treatments, but due to the early phases of development, depending on the outcome of the clinical trials, they are unlikely to be available for clinical use for several years.

4.5 OTHER DEVELOPMENTS

4.5.1 EARLY DEVELOPMENTS

We identified 11 technologies that were very early in development (Appendix 5 Table 5), including a new engineered virus (number 33) and nanoparticle carrier (number 35) for potentially more effective gene therapy delivery, NS2 eye drops (number 36) for Stargardt disease and 3D printing of retinal cells (number 39).

Researchers have created an altered form of vitamin A (number 32) that appears to slow the formation of vitamin A dimers in the eye when given to mice with the same genetic defect as humans with Stargardt disease. Studies have suggested that 'clumping' (deposits) of vitamin A (known as vitamin A dimers) in the retina may be associated with this condition. An expert indicated that ALK-001 (number 31), an oral compound designed to prevent the formation of toxic vitamin A dimers in the eye, also has therapeutic potential in patients with Stargardt disease. Experts commented that both of these technologies have a good scientific basis and need to be assessed in clinical trials.

4.5.2 ALTERNATIVE THERAPIES

Some patients have reported benefits from alternative therapies such as acupuncture and nutritional supplements. Alternative therapies may be popular with some patients as they may improve subjective feelings of well being and give people the opportunity to feel that they are able to do something to take control of their condition. However, alternative therapies generally aim to manage a person's physical and emotional health in a holistic manner, rather than treat the specific condition. There is not enough research to show how effective they are at present.

Some research has suggested that vitamin A may have a beneficial effect for some people with retinitis pigmentosa. The positive effects observed in studies were slight, there is the potential for liver toxicity and teratogenicity, and it is not currently prescribed by most specialists. Other studies are investigating the benefits of mixtures

of nutritional supplements, which may have an anti-oxidant effect and slow retinal degeneration. Examples include saffron[9] and a supplement called Retinacomplex®[10].

5. DISCUSSION

A total of 40 technologies were identified and included in this review. Advice was sought from clinical experts and patient focus groups as to their degree of innovation, potential for future impact (on patient outcomes, NHS systems and resources), current use, and any potential barriers to adoption. The vast majority of these technologies are subject to ongoing or anticipated clinical trials; very few as yet are treatments that are available in clinical practice.

Some technologies are more applicable to earlier stages of disease such as gene therapy, while others are more applicable to advanced stages such as artificial vision and stem cell therapy. According to clinical experts, these treatments are not mutually exclusive and may be complementary, potentially used either together or sequentially.

We identified a number of innovative retinal implants that demonstrate potential in restoring vision. Early trials have shown patients with these devices can have some restoration of vision, although currently the best visual acuity is in the range of about 20/600 to 20/1200, and these devices provide a small field of vision. This level of vision can aid navigation, as well as recognition and localisation of large objects. The Alpha IMS intraocular photodiode implant is perhaps considered the most successful available device for vision restoration potential and long-term biocompatibility[6]. Clinical trials have demonstrated increased patient independence by mimicking natural vision under control of eye movement[5]. Patients may prefer intraocular image acquisition to an external camera[5]. According to the clinical experts, advances in nanotechnology and electronics will result in more sophisticated and higher-resolution devices over time.

Clinical expert and patient opinion indicates that the technologies likely to have the most impact in the future are gene therapies and regenerative and cell therapies. Gene therapy is the most advanced in terms of development and promises both a reduced risk of side effects and the potential for long term efficacy following a single administration of a vector that could be much more cost effective than repeated drug administrations. Most inherited retinal degenerations result from mutations in photoreceptor-specific genes and gene therapy research could expand the range of retinal disorders potentially amenable to this approach.

However, gene therapy approaches are most suitable for treating disorders before the degenerative process has resulted in extensive retinal cell loss. In addition, there are many retinal disorders that are not currently suitable for gene therapy. In later stage disease, blindness results from the death of retinal neurons, rather than loss of function of retinal neurons seen in early stages of disease, so an alternative approach is to replace lost photoreceptors or ganglion cells using cell transplantation. Although ganglion cell replacement might be possible in the future, appropriate regeneration of the long axonal projections to the brain presents a major challenge that has not yet been addressed. According to experts, transplantation of photoreceptor cells has shown promise.

Clinical experts commented that although this is time of great innovation for developing potential treatments for inherited retinal diseases, most of the health technologies

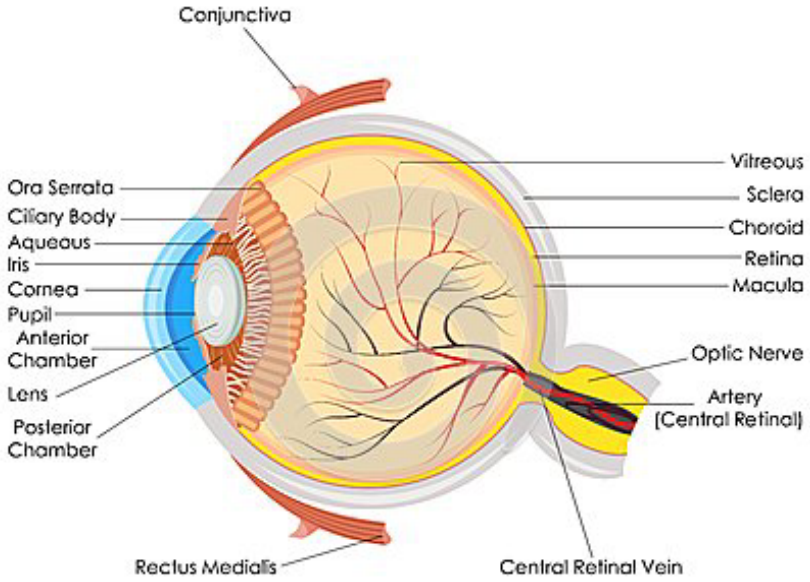
identified in this review are still at an early stage of development. Further well designed trials and data on efficacy, applicability, and costs of the technologies as well as the long term impacts for various conditions are required, before these can be considered for adoption into clinical practice.

In addition, Fight for Sight's patient focus groups highlighted a number of concerns related to the future access to new treatments including:

- Many people with inherited retinal diseases have been discharged from specialist NHS care as they have conditions which are currently incurable and their management is focused on visual rehabilitation, support and training delivered in community settings. This could make it difficult for these people to gain access to new treatments.
- There should be more attention paid to informing clinicians about new developments as and when they become available. There is some concern about availability of treatments being dependent on the awareness of the individual consultant and some people find it difficult to challenge their doctors and what they have been told by them to gain access to new treatments. At present patients feel the onus is largely on them to find out about emerging treatments. ECLOs, patient groups and charities should be made aware of the treatments as they emerge onto the market so they can share the information more widely. There is an extra need for outreach workers to ensure that those of different cultures and ethnicities are included in developments and opportunities, especially for those conditions which are more prevalent in defined ethnic groups.
- New therapies and devices are likely to be expensive and patients expressed concerns that novel treatments will only be made available to younger people, potentially ignoring the needs of older people.

6. APPENDICES

Appendix 1 - Internal structure of the human eye



dreamstime.com©

Appendix 2 - Brief descriptions of selected hereditary retinal diseases[3,11,12]

Condition	Description
Achromatopsia	Achromatopsia is a non-progressive hereditary retinal disorder characterised by decreased vision, light sensitivity and the absence of colour vision. Children with complete achromatopsia will have reduced vision (20/200 or less) due to a lack of cone photoreceptor function. They also have no colour vision, sensitivity to light (photophobia) and the presence of nystagmus (shaking of the eyes). Children with incomplete achromatopsia may have better vision (20/120 to 20/80). This condition affects approximately one in 340,000 live births. Its prevalence varies in different parts of the world. Faults in five genes have been identified to date.
Choroideremia	Choroideremia is a rare inherited disorder that causes progressive loss of vision due to the degeneration of the choroid and of layers of the retina including the retinal pigment epithelium (RPE) and photoreceptors. The choroid provides the RPE and the photoreceptors with nourishment, including oxygen. When the choroid and the RPE degenerate this prevents the photoreceptors from fulfilling their function of capturing light rays and converting them to electrical impulses to be transmitted to the brain. Choroideremia is genetically passed through families by the X-linked pattern of inheritance. As such, the condition almost exclusively manifests in males.
Cone dystrophies (progressive)	This heterogeneous group of rare disorders encompasses a range of problems from pure cone dysfunction to those with varying degrees of associated (but usually less severe) rod dysfunction. Many patients start with a pure cone problem which then progressively affects the rods over time. Presentation is 10 to 30 years old with slow, progressive, bilateral visual loss (night vision better than day), photophobia, poor colour vision ± nystagmus. There may also be associated visual field defects.
Leber's congenital amaurosis	This is an early onset severe retinal dystrophy, which is usually isolated but may be syndromic. Children may have high hypermetropia, keratoconus (cone-shaped cornea), early cataracts, and nystagmus. Presentation - children have severe visual impairment from birth or early infancy. They may exhibit the 'oculodigital syndrome': constant rubbing of the eyes results in orbital fat resorption and subsequent enophthalmos (eyes sunken into sockets). Prognosis is poor.
Retinitis pigmentosa (RP)	Prevalence is approximately 1 in 3,500. Usually isolated but may be syndromic (e.g. Usher Syndrome). Presentation - symptoms often start in childhood with impaired night vision (nyctalopia) or dark adaptation. Progressive loss of peripheral vision is common (resulting in a tendency to trip over things), there may also be loss of central vision, but this tends to occur later. The symptoms usually become apparent between the ages of 10 and 30 years. Prognosis: sight loss is gradual but progresses over a period of many years. Some people with RP may become blind, but most keep some useful vision well into old age. There is no treatment available to cure or prevent the progression of RP.

Stargardt disease	This is the most common form of inherited juvenile macular degeneration and accounts for 7% of all retinal dystrophies. Disease presentation is either in childhood or early adulthood, with bilateral decreased central vision. There is also progressive colour blindness. Prognosis is generally poor.
Usher syndrome	Combination of visual impairment (due to RP) and hearing loss, and there may also be vestibular dysfunction (balance disorder). Deafness is usually congenital but loss of visual acuity and visual field, progressing to severe visual impairment, occurs in the teens and 20s in both Usher syndrome type 1 (USH1) and Usher syndrome type 2 (USH2). The incidence is about 1 in 25,000. About 3-6% of hearing impaired children have the condition. It is autosomal recessive.

Appendix 3 - Search strategy

Identification sources

Source name	Website
Clinical trial and research registers	
ClinicalTrials.gov	http://www.clinicaltrials.gov
Current Controlled Trials	http://www.controlled-trials.com/mrct/
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/
NIHR Research Register	http://www.nihr.ac.uk/databases/Pages/default.aspx
World health organisation (WHO) International Clinical Trials Registry	http://www.who.int/trialsearch/Default.aspx
Media and industry news	
Clinica MedTech Intelligence	http://www.clinica.co.uk/
MedGadget	http://www.medgadget.com/
MEDICA	http://www.medica.de/
Medical News Today	http://www.medicalnewstoday.com/
Primary research and online libraries	
Google Scholar	http://scholar.google.com/
Medline, Medline in Progress and EMBASE	http://www.elibrary.bham.ac.uk/
PubMed.gov	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed
ZETOC – British Library Database	http://zetoc.mimas.ac.uk/
Specialist sources	
EuroStemCell	http://www.eurostemcell.org/
London Project to Cure Blindness	www.thelondonproject.org
Moorfields Eye Hospital Trust	http://www.moorfields.nhs.uk/Home
NIHR Rare Diseases Translational Research Collaboration	https://www.gov.uk/government/publications/rare-diseases-strategy
RETINA	http://journals.lww.com/retinajournal/Pages/default.aspx
The European Blind Union	http://www.euroblind.org
Technology-based sources	
Adis Insight	http://bi.adisinsight.com/
Citeline Pharmaprojects	n/a
Google	http://www.google.co.uk/
National Institute for Health Research (NIHR) Horizon Scanning Centre (HSC) -	Internal database is not publicly available.

database and previous reports	http://www.hsc.nihr.ac.uk/
Tertiary sources, horizon scanning and health technology assessment (HTA) agencies	
Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) and New and Emerging Techniques - Surgical (NETS)	http://www.surgeons.org
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca
ECRI Institute	http://www.ecri.org
EuroScan International Network	http://www.euroscan.org.uk
Health Policy Advisory Committee on Technology (HealthPACT)	http://www.health.qld.gov.au/healthpact/html
International Network of Agencies for Health Technology Assessment (INAHTA)	http://www.inahta.org/HTA/Database/
NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)	www.netscc.ac.uk

Search terms

Inherited retinal diseases		**Technology type**	**Purpose**	**Timeframe**
Achromatopsia	Juvenile macular dystrophy	Advanced (regenerative) therapies	Slow/stop disease progression	New
Adult vitelliform macular dystrophy	Leber's congenital amaurosis	Gene therapy	Reverse sight loss	Emerging
Alström syndrome	Retinal dystrophy	Medical device	Restore sight/vision	
Bardet–Biedl syndrome (BBS)	Retinitis pigmentosa (RP)	Pharmaceuticals/drugs		
Best disease	Sorsby macular dystrophy	Medical technology (medtech)		
Choroideremia	Stargardt's disease			
Cone dystrophies	Usher syndrome			
Fundus flavimaculatus				
MeSH headings: Eye diseases, hereditary; Retinal diseases				

Appendix 4 - Clinical development process

The general clinical development (and implementation) process for health technologies is outlined below[13]. This is applicable to both pharmacological and medical technologies, although they are regulated differently.

Clinical testing of an experimental therapy in humans (or 'clinical trials') is usually divided into three different 'phases' as more patients are recruited and the focus shifts from initial safety testing to studying the effectiveness of a therapy.

<table>
<tr><td colspan="2">IDEA OR INVENTION</td></tr>
<tr><td rowspan="3">CLINICAL DEVELOPMENT & ADOPTION
Putting the new health technology into practice</td><td>Pre-clinical - a new experimental therapy (or prototype) is first tested in the laboratory and then in animal studies. After this 'pre-clinical' testing and only if shown to meet certain safety criteria and have value as a potential new therapy, the health technology advances to clinical testing in humans.</td></tr>
<tr><td>Phase 1 (PI) - can be the first time an experimental therapy is given to humans and usually focus on safety rather than efficacy. Usually involve a small number of patients.</td></tr>
<tr><td>Phase 2 (PII) - trials usually give the first assessment of the effectiveness of an experimental therapy in humans. Information about the experimental therapy's safety, side effects and potential risks are also collected. Researchers try to find the most effective dose and method of delivery. Usually involve larger number of patients.</td></tr>
<tr><td></td><td>Phase 3 (PIII) - these trials use the results of earlier trials to test the experimental therapy in much larger groups of people, gathering additional information on the effectiveness and safety. For pharmacological technologies this phase will usually involve several hundred to several thousand participants across multiple study locations. These trials compare the experimental therapy to another therapy (current therapy) or a placebo (the 'comparator') and might be randomised so that the participants are allocated to receive the experimental therapy or comparator by chance.</td></tr>
<tr><td colspan="2">DIFFUSION
Widespread use in clinical practice</td></tr>
</table>

Appendix 5 - Complete list of technologies identified with clinical experts and patient focus groups comments

Table 1: Gene therapy

No.	Name	Patient group	Developer	Technology description	Development stage	Useful links	Comments from clinical experts and/or patient focus groups
1	**Gene Therapy AAV.REP1**	Choroideremia	Nightstar, a University of Oxford spin-out company; Isis Innovation	Therapy uses a small modified virus called AAV.REP1 to deliver the correct version of the choroideremia (CHM) gene to cells in the retina of the eye. Subretinal injection.	Phase I/II (patients = 12)	http://clinicaltrials.gov/show/NCT01461213	**Expert:** Potential to slow retinal degeneration but trial is at an early stage and longer term follow up (2-4 years) is needed. If the trial shows benefit in terms of slowing retinal degeneration, a randomised trial will be needed.
2	**Gene transfer AAV2-hRPE65v2**	Leber's Congenital Amaurosis (LCA2)	Children's Hospital of Philadelphia; Spark Therapeutics	Subretinal administration of AAV2-hRPE65v2.	Phase III (RCT) (patients = 24)	http://clinicaltrials.gov/ct2/show/NCT00999609?term=NCT00999609&rank=1 http://www.ncbi.nlm.nih.gov/pubmed/22323828?dopt=Abstract	**Expert 1:** Gene replacement therapy in patients with RPE65 deficiency has been shown to improve retinal function in some subjects but may not slow degeneration. Also the improvement in visual acuity is very limited. The authors have reported that younger patients benefit more from treatment. This phase III trial may give better information about the magnitude and the duration of any treatment effect. **Expert 2:** There will be pressure for the patients to be referred to major specialist centres. The NHS will need to make sure that patients can be referred across borders.

3	**Gene Therapy AAV2/2-hRPE65p-hRPE65**	Leber's Congenital Amaurosis	AmpliPhi Biosciences (formerly Targeted Genetics)	Subretinal administration of a recombinant adeno-associated viral vector (rAAV 2/2.hRPE65p.hRPE65).	Phase I/II (patients = 12)	http://clinicaltrials.gov/show/NCT00643747 http://www.ncbi.nlm.nih.gov/pubmed/18441371?dopt=Abstract	**Expert 1:** There is one publication of the first three subjects where there is retinal improvement in one. A further phase I/II trial is planned with a new vector in the next 1-2 years. **Expert 2:** Needs to translate into UK NHS use if safe and effective.
4	**Gene therapy (RPE65 mutation)**	Leber's Congenital Amaurosis	Nantes University Hospital	Subretinal administration of rAAV-2/4.hRPE65 to individuals with RPE65-associated retinal disease.	Phase I/II (patients = 9)	http://clinicaltrials.gov/show/NCT01496040	**Expert:** This trial is similar to the previous studies on gene therapy for RPE65 deficiency, but started later. It is doubtful if the results will be any different to the other trials.
5	**Gene therapy rAAV2-CB-hRPE65**	Leber's Congenital Amaurosis	Applied Genetic Technologies Corp	Subretinal administration of rAAV2-CB-hRPE65 to individuals with RPE65-associated retinal disease.	Phase I/II (patients = 12)	http://clinicaltrials.gov/ct2/show/NCT00749957?term=NCT00749957&rank=1	**Expert:** This trial is similar to the previous studies on gene therapy for RPE65 deficiency, but started later. It is doubtful if the results will be any different to the other trials.
6	**Gene therapy rAAV2-CBSB-hRPE65**	Leber's Congenital Amaurosis	University of Pennsyl-vania	Subretinal administration of rAAV2-CBSB-hRPE65 to individuals with RPE65-associated retinal disease.	Phase I/II (patients = 15)	http://clinicaltrials.gov/show/NCT00481546 http://www.ncbi.nlm.nih.gov/pubmed/21911650?dopt=Abstract	**Expert:** The effects on visual acuity were limited, but there was evidence for improved rod and cone photoreceptor function. They have highlighted the fact that even in subjects with significant improvement in retinal function the treatment did not appear to slow degeneration.
7	**Gene therapy rAAV2-VMD2-**	Retinitis pigmentosa - retinal disease due to MERTK	King Khaled Eye Specialist Hospital	Ocular subretinal injection rAAV2-VMD2-hMERTK gene vector to patients with retinal	Phase I/II (patients = 6)	http://clinicaltrials.gov/show/NCT01482195	**Expert:** Recessive mutations in MERTK cause an early childhood form of retinal dystrophy which is severe. It is not a great candidate

	hMERTK	mutations		disease due to MERTK mutations.			for gene therapy as most patients are severe when they present.
8	**Gene replacement - UshStat; StarGen; MY07A**	Retinitis pigmentosa associated with Usher Syndrome Type 1B	Oxford BioMedica; Collab - Casey Eye Institute (US); licensee Sanofi	Gene transfer agent will be injected subretinally once and only under one retina by an ophthalmic surgeon under anaesthesia.	Phase I/II (patients = 18)	http://clinicaltrials.gov/show/NCT01505062 http://www.oxfordbiomedica.co.uk/clinical-trials-1/	**Expert:** No safety concerns reported to date.
9	**StarGen™ using LentiVector® technology to deliver a healthy copy of the ABCR gene to the retina**	Stargardt macular degeneration	Oxford Biomedica; licensee Sanofi	Subretinally injected StarGen transfer agent.	Phase I/II (patients = 28)	http://clinicaltrials.gov/ct2/show/NCT01367444?term=NCT01367444&rank=1 http://www.oxfordbiomedica.co.uk/clinical-trials-1/	**Expert:** No safety concerns reported to date.

Table 2: Medical technologies

No.	Name	Patient group	Developer	Description	Development stage	Useful links	Comments from clinical experts and/or patient focus groups
10	**Alpha IMS Implant**	Retinitis pigmentosa	Retina Implant AG	Implant to restore moderate sight. System captures light on a wireless subretinal microchip and stimulates the optic nerve based on	CE marked and available for use. 36 people have received the implant.	http://www.hsc.nihr.ac.uk/topics/alpha-ims-for-blind-retinitis-pigmentosa/	**Expert:** Latest study involving 9 blind people showed that the system is a practical solution to restoring useful vision in select patients, as they were able to recognise numbers on doors,

				what the chip sees. Does not use an external camera, so looking around is done naturally with the eyes rather than the head. 1500 photodiodes.		http://retina-implant.de/en/default.aspx	faces, and identify facial expressions. **Patients:** Interesting and innovative area.
11	**ARGUS II Retinal Prosthesis System**	Retinitis pigmentosa	Second Sight	Implant is designed to sit on the surface of the retina (epiretinal) and stimulate the healthy cells of the retina. The implant receives information from a hand held video processing unit, which in turn receives signals from a miniature video camera housed in a pair of glasses. 60 electrodes.	CE marked and available for use. FDA approved.	http://2-sight.eu/en/product-en http://www.hsc.nihr.ac.uk/topics/updated-argus-iiandtrade-retinal-prosthesis-system/	**Expert:** 30 patients have received the implant so far.
12	**Bionic Vision's High-Acuity device**	Retinitis pigmentosa	Bionic Vision Australia	Bionic eye system consists of a small digital camera, external processor and an implant with a microchip and stimulating electrodes surgically placed in the back of the eye. The High-Acuity device will use 1,024 electrodes to stimulate the retina. Aim is to provide more detailed central vision, helping people recognise faces and read large	Not yet CE marked.	http://bionicvision.org.au/eye	No specific comments.

				print.			
13	**Bionic Vision's Wide-View device**	Retinitis pigmentosa	Bionic Vision Australia	Wide-View will use 98 electrodes to stimulate the nerve cells in the back of the eye. Aim is to assist people with profound vision loss see the contrast between light and dark shapes, identify large objects and obstacles.	Not yet CE marked.	http://bionicvision.org.au/eye	No specific comments.
14	**Bionic Eye Technologies Retinal Prosthesis**	Retinal degenerations e.g. retinitis pigmentosa	The Boston Retinal Implant Project; Bionic Eye Tech-nologies	Subretinal implant has stimulating electrodes close to the retinal nerve cells, which should improve the safety of the device and enhance the visual outcome. 1000 electrodes.	Clinical study planned for 2014.	http://www.bostonretinalimplant.org/	No specific comments.
15	**Image Processing Retinal Implant System (EPI-RET Project)**	Retinitis pigmentosa	University of Bonn, Germany. Intelligent Implants GmbH	Epiretinal implant - a camera feeds information to a 'retina encoder' where software mimics the image processing undertaken by the retina. Over time, the system learns to produce a signal that provides a more accurate picture to the patient's brain. 25 electrodes.	System has undergone trials in 50 sighted people.	http://www.nero.uni-bonn.de/projekte/ri/ri-index-en.htm http://abstracts.iovs.org/cgi/content/abstract/43/12/2848	No specific comments.
16	**IRIS2 System**	Retinal degenerations e.g. retinitis pigmentosa	Pixium Vision	Epiretinal implant - a new type of 'neuromorphic' camera system which feeds information to the	Patient testing in 2014, and CE mark expected in	http://www.pixium-vision.com/en/iris2	No specific comments.

				patient's retina when something in the field of vision changes.	early 2015.		
17	**Okustim® System - Transcorneal Electrical Stimulation (TES)**	Retinitis pigmentosa	Okuvision GmbH; Oxford University	Research has shown that TES improves retinal cell viability and visual function. OkuStim device stimulates the patient's eyes with a low current. An initial pilot study of OkuStim on 24 participants with retinitis pigmentosa demonstrated that it was safe and improved vision.	Available for research use in UK.	http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=14217	**Expert 1:** This approach has little scientific basis - we will need to wait for the results of the trials. **Expert 2:** Needs more work and await the results. **Patients:** Could be promising if it gives good improvement to sight.
18	**Smart-Glasses - depth based visual aid**	Visual impairment	Assisted Vision (a spin out company from the University of Oxford)	The glasses have video cameras mounted at the corners to capture what the wearer is looking at, while a display of tiny lights embedded in the see-through lenses of the glasses feedback extra information about objects, people or obstacles in view.	Estimated timeframe for CE marking Q3 2014 and availability for clinical use in October 2014.	http://www.hsc.nihr.ac.uk/topics/smart-glasses-depth-based-visual-aids-for-the-part/	**Experts and patients** agreed that this is an aid or assistive technology. Some doubts expressed over whether this technology would be practical and acceptable, and therefore whether it would be widely used.
19	**Stanford Implant Photovoltaic Retinal Prosthesis**	Retinitis pigmentosa	Stanford University	Sub-retinal implant and uses a specially designed pair of goggles equipped with a miniature camera and a pocket PC that is designed to process visual data. The resulting images would be displayed on a liquid crystal microdisplay	Researchers are hoping to find a sponsor to support tests in humans.	http://www.stanford.edu/~palanker/lab/retinalpros.html http://med.stanford.edu/ism/2012/may/retina.html	**Experts and patients:** Difficult to know if this will work without further work and publication of results. Some doubts expressed over whether this technology would be practical and acceptable, and therefore whether it would be widely used e.g. patients unsure whether they would want to wear 'video

				embedded in the goggles, similar to what's used in video goggles for gaming. Images would be beamed from the LCD using laser pulses of near-infrared light to photovoltaic silicon chip implanted beneath the retina. Electric currents from the photodiodes on the chip would then trigger signals in the retina, which then flow to the brain, enabling a patient to regain vision.			gaming' style goggles in public.

Table 3: Pharmacological technologies

No.	Name	Patient group	Developer	Description	Development stage	Useful links	Comments from clinical experts and/or patient focus groups
20	**Brimonidine Intravitreal Implant**	Retinitis pigmentosa	Pfizer (originator); Allergan (licensee)	Implant formulation for sustained release.	Phase I/II (patients = 21)	http://clinicaltrials.gov/show/NCT00661479	**Expert:** No evidence that brimonidine given topically has a protective effect in RP, so it seems odd to proceed with an intravitreal study. Need to wait for the trial results.
21	**Fenretinide (RT-101) an inhibitor of vitamin A delivery to the RPE**	Dry age related macular degeneration ; Stargardt disease (see additional information)	ReVision Thera-peutics	Oral retinol binding protein inhibitor, thought to prevent the accumulation of retinol toxins in the lining of the retina that may be responsible for loss of vision.	Phase II	http://clinicaltrials.gov/ct2/show/NCT00429936?term=NCT00429936&rank=1	**Clinical expert opinion** suggests it may be worthy of investigation in Stargardt disease. Not well tolerated in age related macular degeneration.
22	**QLT091001**	Leber's	QLT	QLT091001 is a	Phase I/II	http://clinicaltr	No specific comments.

	(oral); synthetic retinaldehyde	Congenital Amaurosis (LCA) or RP due to RPE65 or LRAT deficiency		synthetic retinoid replacement for 11-cis-retinal (the precursor of 11-cis-retinal is Vitamin A). It is an investigational product under development for the treatment of retinal diseases caused by gene mutations that interfere with the availability of 11-cis-retinal. It aims to facilitate recovery or restoration of visual function by acting as a replacement for missing 11-cis-retinal.	(patients = 28)	ials.gov/show/NCT01014052 http://clinicaltrials.gov/ct2/show/NCT01521793?term=NCT01521793&rank=1 http://www.qltinc.com/development/products/QLT091001.htm	
23	**Rescula (isopropyl unoprostone) ;Ocuseva eye drops**	Retinitis pigmentosa	Sucampo Pharma Europe Ltd; R-Tech Ueno Ltd (Japan)	Isopropyl unoprostone (IU) is a maxi-K channel activator, used topically to treat glaucoma, and has been reported to have neuroprotective effects on retinal neurons.	Phase III (patients = 30)	http://www.ncbi.nlm.nih.gov/pubmed/23514642 http://link.springer.com/article/10.1007%2Fs40123-012-0005-9#	**Expert:** will need to wait for the results of the trial. Trials of neuroprotective agents are difficult to do because of numbers of subjects and the long term follow up needed.
24	**Valproic Acid (VPA); oral**	Retinitis pigmentosa	Foundation Fighting Blindness Clinical Research Institute	Research has shown that VPA has an effect on reducing inflammation that results when nerve cells are damaged. Researchers have tested the ability of VPA to associate with rhodopsin,	Phase II (estimated enrolment in trial = 90)	http://clinicaltrials.gov/ct2/show/NCT01233609?term=NCT01233609&rank=1 http://www.nc	**Expert:** will need to wait for the results of the trial.

				a light sensitive pigment found in the outer segment of rod photoreceptors. Some forms of retinitis pigmentosa are caused by mutations in opsin genes, resulting in poorly formed or shaped proteins that are not transported correctly within the cell because they are unable to bind to the chaperone proteins responsible for delivering opsins to their proper position within the photoreceptor.		bi.nlm.nih.gov/pubmed/20647559	

Table 4: Regenerative and cell therapies

No.	Name	Patient group	Developer	Description	Development stage	Useful links	Comments from clinical experts and/or patient focus groups
25	**NT-501 (ciliary neurotrophic factor) implant**	Retinitis pigmentosa (early and late stage); Usher Syndrome; choroideremia	Neurotech USA, Inc.	NT-501 is an intraocular, polymer implant containing human retinal epithelial cells genetically modified to secrete Ciliary Neurotrophic Factor (CNTF). The implant is designed to continuously release CNTF directly into the back of the eye for sustained periods of	Phase II/III (patient = 16)	http://clinicaltrials.gov/ct2/show/NCT00447980?term=NT-501&rank=6 http://www.neurotechusa.com/news_press_releases/pr_2007	**Experts:** According to the clinical experts, recent results of the trial have been disappointing. One expert commented that in their view, it is unlikely to be developed as a treatment. **Patients:** Exciting and in the later stages of development.

				time. CNTF is thought to activate dying retinal photoreceptors and protect them from degeneration. It is inserted during a 15 minute procedure.		-04-17.html	
26	**Human embryonic stem cell (hESC)-derived retinal pigment epithelium (RPE) cells**	Stargardt macular dystrophy	Advanced Cell Technology	Europe's first clinical trial to test the safety of using replacement retinal pigment epithelial cells, derived from human embryonic stem cells.	Phase II/III (patient = 16)	http://clinicaltrials.gov/show/NCT01345006 http://clinicaltrials.gov/ct2/show/NCT01469832?term=NCT01469832&rank=1 http://www.bbc.co.uk/news/health-15017664	**Expert:** Safety study only, appears to be safe in the short term. Major issue with this approach is that the vast majority of patients with Stargardt disease who may benefit from stem cell therapy need replacement of both RPE cells and photoreceptors, and this technology only replaces RPE cells. Doubtful that this will be effective clinically for Stargardt disease.
27	**Human embryonic stem cell (hESC)-derived retinal pigment epithelium (RPE) cells**	Retinitis pigmentosa; age related macular degeneration (AMD)	London Project to Cure Blindness; IRIS UCL; in collaboration with Pfizer	Stem cell therapy in development firstly for AMD.	Clinical trial is planned for patients with AMD at first	http://iris.ucl.ac.uk/iris/browse/profile?upi=PJCOF67 http://www.insight.mrc.ac.uk/2014/02/20/pete-coffey-driving-	No specific comments.

						stem-cells-to-the-clinic/	
28	**ReN003 programme (stem cell therapy)**	Retinitis pigmentosa	ReNeuron	ReNeuron's stem cell products are derived from non-embryonic human tissue sources.	Phase I/II (patient enrolment unknown)	http://www.reneuron.com/other-therapeutic-programmes	**Expert:** Long way to go yet. Cell replacement therapy holds out great hope, but much more preclinical work in animal models needed. **Patients:** Uses non-embryonic tissue. Concern that this may limit its use and more could be done if embryos had been used.
29	**Stem Cell Ophthalmology Treatment Study (SCOTS)**	Retinal diseases (and optic nerve); macular degeneration	Retinal Associates of South Florida	Stem cell treatment study sponsored by the National Institutes of Health in the US.	Phase I/II (estimated enrolment = 300)	http://clinicaltrials.gov/ct2/show/NCT01920867 http://www.mdstemcells.com/SCOTSQuestionsonstemcells.html	No specific comments.

Table 5: Technologies identified that do not meet inclusion criteria (pre-clinical or very early clinical trials)

No.	Name	Patient group	Developer	Description	Development stage	Useful links	Comments from clinical experts and/or patient focus groups
30	**ACU-4429; Emixustat Hydrochloride**	Therapeutic potential in Stargardt disease	Acucela	Non-retinoid compound with a unique mode of action in the retinal pigment epithelium, where it modulates the biosynthesis of visual chromophore through	Phase II/III (just for AMD at present)	http://www.acucela.com/Read-About-Us/Press-Releases/Acucela-Otsuka-	**Expert:** Good scientific basis and needs to be assessed in clinical trial.

				its effect on retinal pigment epithelium-specific 65 kDa protein isomerise. Likely to be trialled in Stargardt disease in the near future.		Pharmaceutical-Phase-IIa-Clinical	
31	**ALK-001**	Therapeutic potential in Stargardt disease	Alkeus Pharma-ceuticals	Oral compound specifically designed to prevent the formation of toxic vitamin A dimers in the eye. ALK-001 has been cleared by the FDA to start a clinical trial.	Phase I	http://www.alkeus.com/stargardt.html	**Expert:** Good scientific basis and needs to be assessed in clinical trial.
32	**Altered form of vitamin A that appears to slow the formation of vitamin A dimers in the eye**	Stargardt disease	Columbia's Harkness Eye Institute, US	Studies suggest aggregation or "clumping" of vitamin A in the retina may be associated with Stargardt disease. These clumpy deposits are known as "vitamin A dimers". Researchers created an altered form of vitamin A that appears to slow the formation of vitamin A dimers in the eye when given to mice with the same genetic defect as humans with Stargardt disease.	Pre-clinical	http://techventures.columbia.edu/news/columbia-researchers-work-preventing-blindness-age-related-macular-degeneration-and-stargardt-s	**Expert:** Good scientific basis and needs to be assessed in clinical trial.
33	**Engineered virus for gene therapy**	Retinitis pigmentosa	University of California at Berkeley	Virus injected into the liquid vitreous humor to deliver genes to the	Pre-clinical	http://newscenter.berkeley.edu/2013/06/	**Expert:** Possible improved form of gene delivery, but needs more experimental work.

	delivery			back of the eye to reach the photoreceptors.		12/researchers-develop-easy-and-effective-therapy-to-restore-sight/	
34	**Glial cell and retinal progenitor cells in retina repair**	Retinal diseases	University of Washington	Human embryonic stem cells to generate limited photoreceptors to transplant into mouse models.	Pre-clinical	http://faculty.washington.edu/tomreh/ http://depts.washington.edu/behneuro/people/faculty/reh.shtml	**Expert:** Early phase, needs more preclinical work in animal models.
35	**Nanoparticle gene therapy - non-viral, synthetic nanoparticle carrier**	Retinitis pigmentosa	Dept of Cell Biology, University of Oklahoma Health Sciences Center, US	Non-viral, synthetic nanoparticle carrier to improve and save the sight. Tested in animal models. Researchers found that mice had structural improvement in their retinas, as well as functional vision improvements which lasted throughout the duration of the study.	Pre-clinical	http://www.medgadget.com/?s=inherited+retinal+diseases	**Expert:** Early phase, needs more preclinical work in animal models.
36	**NS2 (eye drop)**	Therapeutic potential in Stargardt disease	Aldexa	NS2 has been shown to bind and trap free aldehydes more rapidly than aldehydes bind cellular constituents. NS2 is generally safe and well-tolerated topically and systemically in animals.	Completed Phase I trial in humans when administered as an eye drop	http://capturinghealth.com/therapeutics/	**Expert:** Has scientific rationale, but needs clinical trial.

37	**Optogenetic therapy**	Retinitis pigmentosa	N/A	Gene delivery of microbial light-activated ionic channels or pumps 'optogenetic proteins' to transform surviving cells into artificial photoreceptors.	Pre-clinical	http://www.ncbi.nlm.nih.gov/pubmed/21993174 http://www.ncbi.nlm.nih.gov/pubmed/24103341	**Expert:** Very early preclinical stage. One of many possible approaches.
38	**Photoreceptor transplantation - embryonic stem cells**	Retinal diseases	UCL Institute of Ophthalmo-logy and Moorfields Eye Hospital	First successful transplant of light-sensitive photoreceptor cells extracted from a synthetic retina, grown 'in a dish' from embryonic stem cells. When transplanted into night-blind mice these cells appeared to develop normally, integrating into the existing retina and forming the nerve connections needed to transmit visual information to the brain.	Pre-clinical	http://www.ucl.ac.uk/news/news-articles/0713/21072013-Scientists-transplant-photoreceptors-from-retina-grown-in-a-dish-Ali	No specific comments.
39	**Piezoelectric inkjet (or '3D') printer**	Glaucoma currently	University of Cambridge, UK	Piezoelectric inkjet printer that can be used to print two types of cells from the retina of adult rats—ganglion cells and glial cells.	Pre-clinical; proof of principle. More development required before human testing.	http://www.cam.ac.uk/research/news/cells-from-the-eye-are-inkjet-printed-for-the-first-time#sthash.Hs22PqpD.d	**Expert:** Interesting idea, but at very early stage. Much more preclinical work to do.

						puf	
40	**VSM 20R - small molecule therapeutic**	Therapeutic potential in Stargardt disease	Visium	In normal vision, absorption of a photon of light initiates a signaling cascade which results in the visual pigment rhodopsin triggering light perception in the brain. In the final stages of the vision cycle, all-trans-retinal (ATR), an intermediary in this process, gets isomerised back to its starting conformation so the vision cycle can begin again. However, in Stargardt's disease ATR is not cleared properly, which leads to the formation and accumulation of cytotoxic metabolites. Visum's approach proposes to develop a drug that will temporarily control levels of ATR.	Pre-clinical	http://www.visumtherapeutics.com/	No specific comments, but suggested by an expert as a technology if interest.

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