Unmet needs in Ophthalmology - An European Vision Institute (EVI)-Consensus Roadmap 2019-2025

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Abstract

**Purpose:** To define unmet needs in ophthalmology which can realistically be addressed in the next five years (2019-2025) and describe potential avenues for research to address these challenges.

**Methods:** Outcomes of a consensus process within the European Vision institute (EVI, Brussels) are outlined. Disease areas which are discussed comprise glaucoma, retinal dystrophies, diabetic retinopathy, dry eye disease, corneal diseases, cataract and refractive surgery.

**Results:** Unmet needs in the mentioned disease areas are discussed and realistically achievable research projects outlined.

**Conclusions:** Considerable progress can be made in the ophthalmic field and patient-relevant outcomes in the near future.
Introduction

Vision is the most important sensory function with >30% of the human brain being involved in processing visual information. Consequently, loss of vision ranks highest in the general population’s fear among all possible disabilities (1). Ophthalmology principally is a very successful part of medicine, where numerous patients can be treated and vision can be restored or maintained in many patients. Nonetheless there are areas where pathophysiological understanding and consequently treatment options are insufficient.

Only research and medical progress can solve these unmet needs. Relevant diseases areas with high prevalence include glaucoma, retinal degenerative diseases, dry eye disease, corneal dystrophies, cataract and refractive diseases.

The European Vision Institute (EVI) is an established “think tank” in ophthalmological research in Europe. As a result of internal discussions we here set out to define unmet needs in ophthalmology which can realistically be achieved within the time frame of 2019-2025.

The unmet needs should guide policy makers, industry and academia in their endeavours to minimize preventable blindness.

Here we outline unmet needs in ophthalmic research in the areas of glaucoma, retinal dystrophies, diabetic retinopathy, dry eye, corneal diseases and cataract as well as refractive surgery and discuss realistically achievable research projects in these areas.
Literature

1. Unmet Needs in Glaucoma

1.1 Non-IOP dependent treatments (especially neuroprotection)

The number of pharmacological agents available to treat glaucoma is limited by the few mechanisms of action currently utilised in glaucoma pharmacotherapy. Currently, these all target intraocular pressure (IOP) via reducing aqueous production or increasing the draining from the eye. However, we know that some patients will have disease progression even though their IOP has been sufficiently lowered\(^1\), and similarly, some patients will not ever present with raised IOP but appear to have progressive glaucoma (‘Normal-tension’ glaucoma)\(^2\). A further subset of patients will either be resistant to topical treatments to lower the pressure in the eye or intolerant of their side effects. All these anomalies suggest the underlying process of neurodegeneration is incompletely targeted by IOP lowering and therefore, pharmacologic strategies to protect against glaucomatous neurodegeneration in an IOP-independent manner are an unmet need. These may provide an early method of preventing the initiation of secondary neurodegenerative processes and also a lifeline for those patients who have no further treatment options.

1.2 Surrogate end points

Progression of glaucoma is often slow, and furthermore can take many years to reliably detect and confirm on visual field testing. If follows that demonstrating the efficacy of novel treatments by showing visual field preservation is a long and expensive task, and often prohibitive in clinical trials. It is for this reason why the majority of clinical trials in glaucoma only use intraocular pressure as their outcome measure, with the visual benefit for the patient assumed via evidence from studies such as the Ocular
Hypertension Treatment Study\textsuperscript{1}. There is an unmet need for surrogate markers to represent progression of glaucoma that can be used as a substitute for visual field testing in order to shorten the duration of clinical trials and make them more cost effective, without compromising on the quality of information gained. The considerable amount of attention being given to imaging biomarkers to fulfil this role has been a promising development over the previous decade\textsuperscript{3}.

1.3 Better outcome measures in clinical trials

The outcome measures in glaucoma are currently suboptimal in a variety of ways. Visual field testing as the current ‘gold-standard’ relies on the patient’s ability to carry out the procedure, requiring a certain amount of learning, physical and mental ability. It is also evident that there is significant delay in the appearance of visual field defects after a considerable loss of retinal nerve fibre layer, at which point neurodegenerative rescue may be less effective\textsuperscript{4}. There is an unmet need for new endpoints that can represent the earliest stages of disease without the need to wait for damage to occur to visual function or structural pathways. Universal biomarkers that encompass patients without raised IOP are likely to be most valuable, such as objective imaging of progressive nerve fibre layer thinning which has a clear pathophysiological involvement in the visual loss experienced in glaucoma\textsuperscript{5}. Future methods of in-vivo cellular and high-magnification imaging are exciting new avenues of investigation that are being explored in order to detect the underlying retinal ganglion cell loss, prior to manifest clinical significance\textsuperscript{6-8}. 
1.4 Early diagnosis with high specificity and sensitivity

The ability to reliably diagnose early glaucoma is an unmet clinical need. The crossover between ocular hypertension and glaucoma results in many patients being followed up and taking daily eyedrops for many years that will not develop clinically significant disease in their lifetime. However, the risk is that if visual loss occurs it is currently irreversible. Several advances have suggested that the current biomarkers can be modified to improve their sensitivity for early disease such as alternative visual field testing protocols and imaging of the macular ganglion and nerve fibre layers, however novel methods have been few and far between. What is being increasingly recognised that may increase the complexity of diagnosis is that glaucoma exists within a spectrum of age-related neurodegenerative conditions including Alzheimer’s disease and Parkinson’s that are also associated with retinal nerve fibre layer thinning, however are unlikely to benefit from the lowering of intraocular pressure.

1.5 IOP telemetry

The use of one-off intraocular pressure measurements in clinical practice is likely to be misleading a variety of scenarios. Firstly, significant variations in IOP occur over seconds, days or months. Therefore, if the clinic appointment is scheduled at a different time of day to the previous appointment, the readings will not be comparable, and furthermore, spikes of high pressure may not be captured within clinic hours. Secondly, many different factors can effect this reading taken in clinic, including the methods or observer used, as well as physiological factors such as postural changes, exercise or some systemic medications. These factors suggests there is an unmet clinical need to widen the availability of continuous intraocular pressure measuring devices that will give the clinician a better idea of the range of IOPs that the optic
nerve is subject to, and a more comprehensive impression of an individuals’ response to a particular treatment.

1.6 More proven (with long term efficacy) MIGs

Operations such as trabeculectomy and tube surgery have been the mainstay of surgical glaucoma management for decades. However, not all patients require such dramatic pressure reductions, and the procedures also come with risk of cataract formation, hypotony and endophthalmitis. Minimally-invasive glaucoma surgery (MIGS) is a surgical field of interest that has been devised to augment cataract surgery\(^{17}\). Given the frequency of cataract operations, the insertion of small devices such as those which bypass the trabecular meshwork\(^{18}\) or drain into the supraciliary space\(^{19}\) have become popular in order to reduce the drop burden for the patient following surgery. However, given the small lumens of such devices, it is imaginable that the lifespan of these conduits is limited, therefore long-term follow-up data is required in order to confirm that these procedures are safe and produce lasting effects. Given the anatomical and pathological variations in angle configuration, there is an unmet need for a wider variety of such surgical procedures to provide long-term IOP lowering effects, and in more complex cases such as angle-closure glaucoma and secondary disease.


2. Unmet needs in Retinal Dystrophies

Inherited retinal degenerative diseases (retinal dystrophies; IRDs) are a genetically and phenotypically heterogeneous group of disorders that affect the function of photoreceptor cells (1). They typically lead to severe visual impairment or blindness early in life, and are the leading cause of legal blindness among working age adults in England and Wales, having replaced diabetic retinopathy (2). Recently, the American Academy of Ophthalmology published recommendations for the clinical assessment of patients with IRDs (3). Therapeutic options are currently limited, as is the case for many neurodegenerative diseases, but new therapeutic approaches including gene therapy, stem cell therapy, optogenetics, and retinal prostheses are on the horizon. Many of these approaches have entered the clinical phase of development and retinal prostheses have received market approval in Europe and the United States (1, 1a, 4) (Figure 1).
Figure 1 (from Ref 4): Current and planned tools for treating blinding diseases. The approximate physical sizes span six log units, and the numbers of tools delivered to the eye span 15 log units. The approximate sizes and numbers of tools delivered are shown below each tool. The complexity and sophistication of the tools increase with size, as does the difficulty of delivering treatment across a large retinal surface in vivo. The characteristics of the different tools are shown below the images.

To date, 271 disease genes have been identified (5). Genetic analysis employing sequencing the coding regions of these gene via panel diagnostics allows to identify the genetic cause in approximately two thirds of patients (6). There is the unmet medical need to improve the sensitivity of testing such that pathogenic mutations are identified in a more substantial fraction of cases, to incorporate improved sequencing methods into research and diagnostic testing, to improve the ability to determine
which rare variants are indeed disease-causing, to identify genetic modifiers of disease severity, and to overall improve access to molecular genetic diagnostic testing, test result evaluation, and genetic counseling, including improved payment mechanisms and more widespread coverage of testing costs (7).

Disease models are needed for the understanding of the pathophysiology and basic mechanisms of IRDs, to identify novel targets for therapy and to provide proof of concept for therapeutic strategies (7). The most widely used mammalian animal model is the mouse. However, there are differences in retinal cell-type composition, in cell-type-specific gene expression, and in the organization of the retina at the macroscopic level that strongly limit the translation of findings to the human situation (4). The use of induced pluripotent stem cells (iPSCs) to grow human retinal organoids has provided a platform to study IRDs for which there is no relevant animal model or for which the human mutations have not been recapitulated in an animal model (4, 7). Further, iPSC models have proven useful in establishing proof of concept when an animal model is absent. For example, the use of iPSC to validate gene augmentation as a therapeutic strategy for choroideremia has resulted in FDA approval of a phase I/II clinical trial (NCT02341807) (7).

The recent FDA approval of gene augmentation therapy for RPE65-associatedIRD using adeno-associated viruses (AAV) is an important milestone and suggests that similar approaches can be used for the treatment of many other genetic forms of IRDs (8). However, cell-specific targeting remains an unmet need, especially since the human retina contains about 100 different cell types that form specific synaptic
connections and reside in functionally distinct microcircuits (9). Along this line, it has very recently been accomplished to develop a library of 230 AAVs, each with a different synthetic promoter, most of them driving an optogenetic tool fused to a fluorescent marker. The marker-tagged optogenetic tool enables cell types to be both identified and manipulated (10). Also, the best way to deliver gene products to the target cells by e.g. subretinal delivery or intravitreal injection remains to be determined (1).

Although it is accepted by clinicians that IRDs are typically progressive, natural history studies are lacking. The ProgStar (11) and RUSH2A studies are examples to study the progression of disease in a multi-center approach. For therapy development and clinical monitoring of patients, there is a need to develop and validate reliable outcome measures, endpoints, and/or biomarkers that may be important targets to monitor and modify both for in the earliest possible stages of the degenerative process and along the disease process in general (7). Such outcome measures or biomarkers must demonstrate change over a relatively short time period spanning no more than 2 to 3 years. This also means that we need visual function tests of foveal vision other than visual acuity. In the ProgStar study, the estimate for the specific Stargardt disease patient population was 27 years to lose 3 lines on a ETDRS visual acuity chart (12). Also, we need an improved understanding of the relationship between photoreceptor structure and visual function with the goal of understanding the relationship between genotype and clinical phenotype and how many photoreceptors and other retinal neurons need to be restored to provide useful vision (7).
References:


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(10) Juettner et al. Targeting neuronal and glial cell types with synthetic promoter AAVs in mice, non-human primates, and humans. bioRxiv 2018 [online].


3. Unmet needs in Diabetic Retinopathy

Diabetic Retinopathy (DR) is a frequent complication of diabetes and through its sight-threatening complications, i.e., macular edema and proliferative retinopathy, may lead to loss of vision. Indeed, DR is the leading cause of vision loss in working age adults (1).

Recent advances in therapy, particularly intravitreal administration of anti-angiogenic agents, have opened new therapeutic perspectives (2,3). However, the availability of treatment only for advanced, sight-threatening stages of the disease and its rate of success make it urgent to understand the initial alterations of DR and their progression in order to be able to treat earlier before vision loss has already occurred (4,5). The challenge is to treat and stop disease progression before complications develop or, at least, as soon as they are expected to occur.

The course of DR is not linear and the progression of DR varies in different individuals with the time necessary for the development of sight-threatening complications being much less in some patients than others. Activity of disease and its progress varies from patient to patient(6).

It is recognized that the duration of diabetes and the level of metabolic control determine the development of DR. However, these risk factors do not explain the great variability that characterizes the evolution and rate of progression of the retinopathy in different diabetic individuals. There are many diabetic patients who, after many years with diabetes, never develop sight-threatening retinal changes, whereas other patients progress rapidly.

We have identified three major phenotypes of DR progression: one, characterized by slow progression, where neurodegeneration may be the only identified alteration; a second one, characterized by occurrence of edema, even in the absence of relevant
microvascular pathology; a third one identified by increased microaneurysm turnover and the presence of active microvascular lesions(7–9). In follow-up studies, the first phenotype only rarely progressed to sight-threatening complications, whereas the second phenotype showed a relatively high risk for development of macular edema, and the third one, shows the higher risk for development of both macular edema and proliferative retinopathy. This phenotype is identified on OCT Angiography (OCTA) by the early presence of retinal capillary dropout (Figure 2). Recent studies by our group indicate that capillary dropout and its extent is the only retinal alteration that is directly correlated with severity of DR(10).

It is becoming clear now that only a subset of patients with diabetes who develop retinal changes is expected to progress to advanced retinopathy stages and be at risk to lose functional vision during their lifetime.
Figure 2: Example for capillary dropout. A-D: SRP and DRP images and skeletonization for vessel density measurements, from a 64-years-old male patient of the ETDRS severity level 43-47 group, showing definite capillary dropout on the SRP and on the DR. E: A B-scan in the central macular area.

Identification of biomarkers of progression of DR to vision-threatening complications is, therefore, a major need. Microaneurysm turnover calculated from fundus photography images and capillary dropout measured by OCTA are major candidates to fulfill this role.

Another need is the validation of biomarkers of visual acuity response to treatment of diabetic macular edema. Identification and quantification of extracellular fluid in the
outer retinal layers show clear potential but further studies are needed as well as practical and improved functional testing of central vision loss (11–14).

It is now becoming clear that ischemia, identified by retinal capillary closure, is the central alteration occurring in DR and the one that determines its progression to more severe stages of the disease (10). Treatments addressing specifically localized ischemia are expected to stabilize the retinopathy and may stop DR progression. Standardisation of OCTA measurements of capillary dropout and ischemia are, therefore, crucial to allow the evaluation of potential drugs and a still unmet need.

Other unmet needs include the identification of the changes that may characterize the eyes with macular edema that will respond to anti-VEGF or steroid intravitreal injections. It is believed that the predominance of localized ischemia or inflammation may determine those eyes that should be more responsive to these different therapies. Again, methods to identify these changes are clearly needed. Vitreous sampling at the time of the injections and rapid analysis of the sample would be ideal if sufficiently safe (15, 16). Analysis of other fluids such as aqueous humor or tears may offer appealing alternatives if they give reliable results (17–19).

References


4. Unmet needs in dry eye disease, ocular surface and corneal disorders

Dry eye disease (1; DED) and corneal diseases encompass the most common eye diseases where patients seek help from their ophthalmologist as well as the second most common form of blindness worldwide (2). Although significant progress has been made in some aspects of the field, several important unmet needs need to be addressed in the next 5 years.

4.1 Dry eye disease

The recent Dry Eye Workshop (DEWS) report (1) outlines current progress in understanding the pathogenesis and therapy of dry eye disease. Important unmet needs to be addressed in the near future are:

- **Optimized topical anti-inflammatory therapy**: Several options for anti-inflammatory therapy including topical (unspecific) steroids, cyclosporine and integrin antagonists are already on the market. Nonetheless better tolerated and more efficient therapies are needed. This may be achieved using different modes of formulation and/or new anti-inflammatory/immunomodulating agents. Progress can be expected from translation in the field of immunomodulation in neurology and internal medicine.

- **Pain relief**: New tools are needed for diagnosis and treatment of peripheral and central neuropathic pain, a novel key feature in dry eye patients (1). Topical and systemic therapies against receptors triggering and processing pain sensation are needed. Readily established systemically applied pain therapies need to be tested for efficacy in ocular pain. A key aspect here is the essential absence of negative effects on epithelial integrity and wound healing. Such compounds would also be very valuable in refractive surgery (see below).
Artificial tears: a plethora of substances is already on the market. There exists a need for a personalized approach to substitute only those tear film layers affected in a given patient, isolated or in combination. This should be preservative free and long lasting. Here unmet needs exist in diagnosing the individual tear film deficiency as well as in an individualized approach to replace these layers affected in a given patient.

Blepharitis/Meibomian gland dysfunction: Meibomian gland dysfunction contributes to 80% of all DED (1). A sufficient anti-inflammatory/lipid-modulating local therapy also allowing for release of Meibomian gland obstruction is still missing. Here again progress could be expected using immunomodulation from the fields of dermatology, neurology and rheumatology.

Biomarkers for diagnosis and monitoring: Identification of biomarkers and surrogate markers and the consecutive development of point-of-care and imaging devices is crucial for better and more precise diagnosing and stratifying subtypes of disease and disease activity. The use of these tools will further allow to adapt treatment options in a personalized manner to each individual patient in each individual phase of disease. In the future this should evolve in self-testing devices for use by the patient at home.

4.2 Cornea

Corneal transplantation has been revolutionized in recent years by the advent of modern lamellar surgical techniques such as DMEK and DALK (3). These allow for safe and efficient restoration of vision in the low-risk scenario e.g. of Fuchs dystrophy and keratoconus with very low rates of immune reactions (4). Unmet needs exist
primarily in the area of vascularized high-risk eyes and eyes with limbal stem cell deficiency.

→ **Topical anti(lymph)angiogenic agents in high-risk eyes to promote graft survival:**

There is compelling evidence from preclinical and early clinical studies suggesting a key role of pathologic corneal hem- and lymphangiogenesis in triggering immune reactions after high-risk transplantation (5). Furthermore, there is clear evidence that targeting these (lymphatic) vessels can promote graft survival (5, 6). Nonetheless there is still no licensed topical inhibitor of (lymph)angiogenesis available for use as eye drops for the anterior eye and ocular surface (7), although certain compounds have already been tested in phase III trials (8). In addition to promoting graft survival, several other indications for topical antiangiogenesis exist at the ocular surface (3,6).

→ **Gene therapy for corneal dystrophies:**

Corneal dystrophies lead to reduced vision, blindness and pain. Although the genetic basis is increasingly better understood (9), current treatments still rely on laser or mechanical surgery and carry the burden of high recurrence rates and costs. Gene therapy e.g. using CRISPR/Cas approaches could be an ideal solution for the treatment of the easily accessible corneal dystrophies.

→ **Antinflammatory and anticollagenolytic therapy e.g. in keratoprosthesis surgery and rheumatic diseases:**

Several systemic vasculitis- and rheumatology-associated diseases are linked to collagenolysis and melting of the peripheral cornea. The same can occur after artificial corneal transplantation (keratoprosthesis). Here an unmet need exist for topically applicable agents preventing keratolysis. Similarly, an unmet need exist for
better tolerated biocorneas to relieve the worldwide donor tissue shortage (see also below; 10).

→ Neurotrophic keratopathy: Nerve growth factor (NGF) and more:

Although with recombinant NGF eye drops a first agent to treat neurotrophic keratopathy (NK) is on the market (11), there is an unmet need for better understanding of NK and for the development of other neurotrophic agents in treatment failures with NGF eye drops. Here again synergies with neurology might help.

→ Therapies against acute and chronic corneal edema:

Although there are surgical approaches for diseases leading to corneal edema and blindness available (DMEK; 3), pharmacologic approaches are missing avoiding the need for transplantation. Recently isolated temporary corneal lymphangiogenesis was shown to lead to expedited recovery of acute cornea edema (12). Here an unmet need exist for the development of topical prolymphangiogenic agents to induce edema drainage from the cornea (Figure 3).
**Figure 3** Transient isolated lymphangiogenesis in acute corneal edema representing a potential new treatment strategy against acute and chronic corneal edema (from ref. 12).

**→ Limbal stem cell deficiency:** Although the concept of (limbal) stem cell transplantation was initially developed in ophthalmology, there is still no commercially available stem cell based therapy, especially not for bilaterally affected patients (13). Progress has been made in characterizing stem cell phenotypes (14). Unmet needs exist in delivering reliable stem cell therapies also for bilateral diseases. In addition, approaches to prevent UV-induced damage to stem cells also in the context of pterygium are needed (15).

**→ Biomaterials for the replacement of diseased corneal tissue:** There is a worldwide shortage of donor tissue (10). Moreover, chronic inflammatory diseases of the cornea and the anterior surface are associated with a high rate of graft failure in almost all variations of corneal tissue transplantation / replacement. There is a high demand for biomaterials that are optically clear, inert to enzymatic degradation and swelling, and that integrate well with diseased corneal tissue.
4.3 Conjunctival diseases

→ Therapies against metastasis and recurrence of squamous cell carcinoma and conjunctival melanoma:

There is currently no therapy against recurrent or metastasing conjunctival malignancies such as squamous cell carcinoma or melanoma. Progress could be made using approaches from oncology outside of the eye, e.g. using murine models (16).

→ Antiinflammatory approaches against cicatricial diseases of the ocular surface (ocular pemphigoid etc):

Several blinding diseases of the eye are associated with conjunctival scarring and inflammation, such as in ocular bullous pemphigoid or Steven Johnson syndrome. Here no effective local anti-inflammatory and/or antifibrotic agent is available. Progress can be made using antifibrotic/antiinflammatory agents from other areas of medicine.

→ Artificial conjunctiva for ocular surface reconstruction: Chronic (autoimmune) inflammatory diseases of the conjunctiva often lead to corneal blindness and are particularly difficult to treat. The accompanying dry eye syndrome prevents a sufficient reconstruction of the corneal surface. New techniques for the generation of conjunctival grafts with low immunologic activity (e.g. autologous cell cultures or cultures from iPSC derived conjunctival epithelial and goblet cells on immunological inert carrier membranes) need further developments before transfer into clinic.
Ref.


3. Hos et al. PRER 2019 in press


5. **Unmet needs in cataract and refractive surgery**

5.1 **In cataract surgery** a spectacular level of safety and efficacy has been achieved in the last decades. Here, realistically addressable unmet needs are

→ **Phenotyping/genotyping of congenital cataracts** to allow for potential pharmacologic or gene therapies.

→ **Presbyopia**: Accommodative lens filling material allowing for presbyopia free vision even after cataract surgery or pharmacologic approaches for (temporary) nearsightedness are needed. Other options include laser-based or corneal shaping-based approaches against presbyopia.

5.2 **Refractive surgery** has achieved an astonishing level of safety and efficacy using Excimer- and Femtosecond laser applications. Nonetheless unmet need exist in the following areas:

→ **Topical pain relief not affecting epithelial healing**: this would allow for a revolution in ocular surface laser ablation avoiding potential flap-based complications.

→ **Non-invasive corneal tissue modelling approaches for customized reshaping of the ocular surface**: e.g. using crosslinking techniques. Here intraoperative OCT-based imaging seems important for monitoring (17).

→ **Standardized therapy for prevention of myopia progression in children**.

**Ref.**

17. Intraoperative changes in corneal structure during excimer laser phototherapeutic keratectomy (PTK) assessed by intraoperative optical coherence tomography.
Siebelmann S, Horstmann J, Scholz P, Bachmann B, Matthaei M, Hermann M,