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Clinical characteristics and management of retinitis pigmentosa

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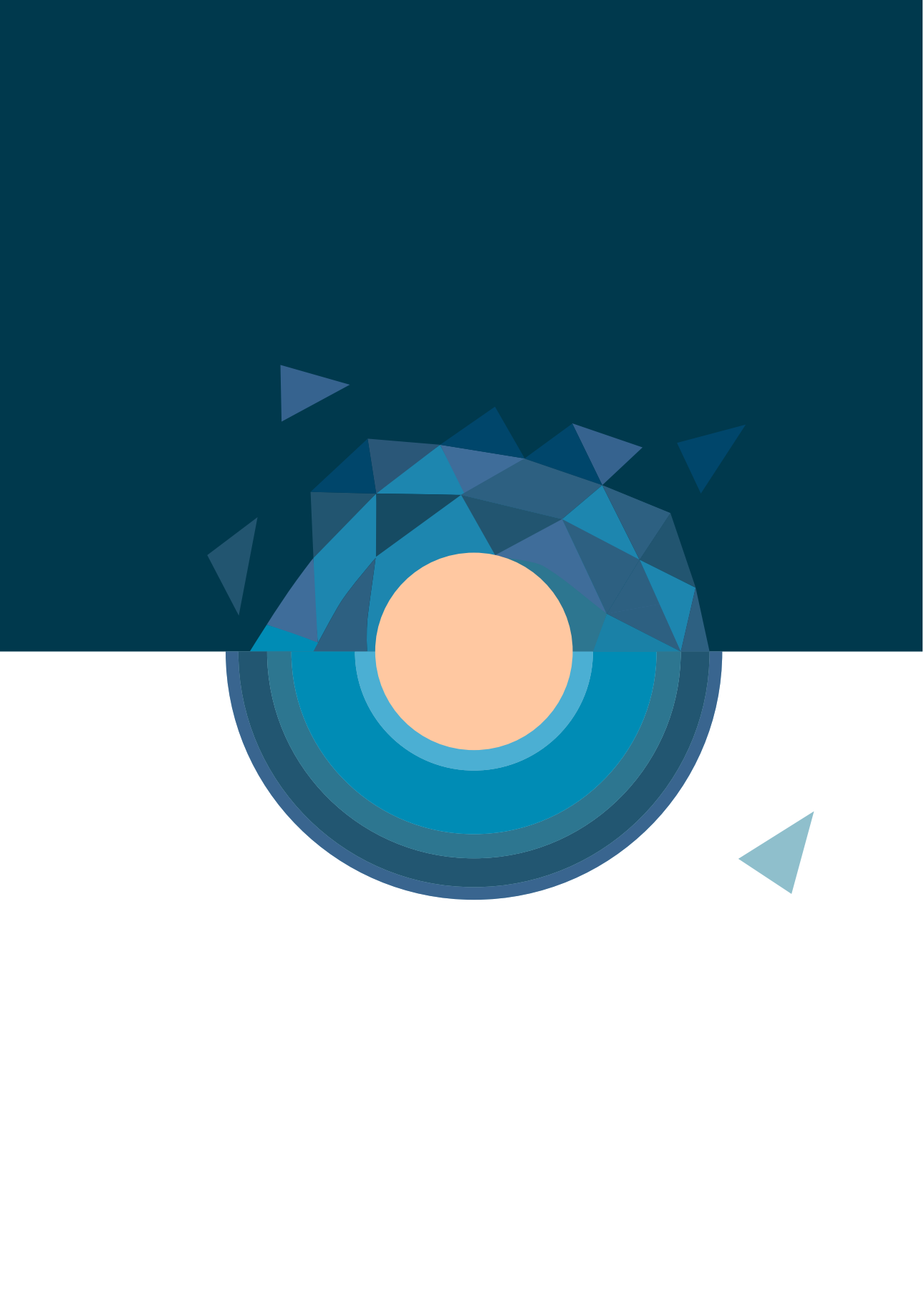

CHAPTER 4

GENERAL DISCUSSION

Partly adapted from:

Retinitis Pigmentosa: Current Clinical Management and Emerging Therapies
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GENERAL DISCUSSION

In view of current and future clinical trials, this thesis aims to provide a better understanding of the clinical and genetic characteristics of several subtypes of RP. An in-depth knowledge on the natural history of RP is important for trials and often required by regulatory agencies to determine the appropriate patient sample size, and to determine sensitive endpoints. By comparing treated and non-treated eyes, treatment efficacy and safety may be evaluated. Moreover, surrogate endpoints or biomarkers may also be identified based on these natural history studies, which can accelerate the measurement of progression or treatment response.

In this thesis, we also explored the benefit of several treatment or supportive options that are currently available for RP. In this exciting era of emerging gene therapy, it remains imperative to continue supporting patients with RP using all available options to manage their condition. Patients with a progressive retinal disease such as RP may experience a wide variety of physical, mental and social-emotional challenges over time that need to be timely addressed if possible.

Below, the findings of our previous chapters are discussed, and we explore current management options and future perspectives.

CLINICAL CHARACTERISTICS AND NATURAL HISTORY STUDIES

The natural course of *RHO*-associated RP indicates the need for surrogate endpoints

The *RHO* gene was the first causal gene to be linked with RP.[1] *RHO* encodes the rod visual pigment rhodopsin that is located in the outer segments of rod photoreceptors. To date, over 150 variants have been found associated with *RHO*-associated RP, and this gene is responsible for over 30% of all cases of autosomal dominant RP. Variants in *RHO* are not only associated with generalized RP, but can also cause sectorial RP, and rarely congenital stationary night blindness.[2] The protein rhodopsin has been thoroughly investigated, and it has been highly suggested that variants in specific protein domains have distinct consequences on the protein's structure and function.[2]

In **Chapter 2.1**., the phenotype and genotype of patients with *RHO*-associated RP were characterized, based on one of the largest cohorts to date. Two separate phenotypes were present in the study: generalized RP and sectorial RP, the latter characterized by retinal degeneration confined to the inferior quadrant of the retina.[3] In patients with generalized RP, visual function was relatively preserved, as the first occurrences of low vision, several visual impairment and blindness based on BCVA or VF were observed from the 5th decade onward in patients with generalized RP. This was even later for

patients with sector RP, with the first instance of blindness found in the 8th decade of life. This is in line with previous studies, suggesting that *RHO* has slower disease course with a more favorable visual prognosis compared to other genetic subtypes of RP.

A slow disease course is also favorable with respect to therapies, as it means that there is a broader window for therapeutic intervention. Based on the occurrence of visual impairment in our study, we proposed that the optimal window for intervention in *RHO*-associated RP is before the 5th decade of life.

In the context of developing future therapies, the use of surrogate markers is an important factor to consider. Since *RHO*-associated RP is a disease that progresses slowly based on BCVA and VF, it would be challenging to demonstrate treatment efficacy using these conventional outcome measures. Clinical trials are typically conducted in a period between 2 to 4 years. Based on our studies, we suggest that the outer retinal thickness may be used as a surrogate outcome measure, because it highly correlated with visual acuity. Surrogate markers may facilitate the measurement of change within a shorter period of time, which can be particularly helpful for relatively slowly-progressing IRDs such as *RHO*-associated RP.

***RPGR*-associated retinal dystrophies: clinical and histopathological features**

Variants in *RPGR* are the major genetic cause of XLRP (70-90%), and XLRP is considered one of the most severe forms of RP. While young males are typically affected, clinical symptoms and fundus findings may also be present in female carriers.[4] Both RP and CRD phenotypes have been described, with the latter typically found in the mutational hotspot ORF15.

In **Chapter 2.2**, we report the early onset of symptoms in patients with *RPGR*-associated RP, and a much later symptom onset in patients with CRD. Multimodal imaging revealed a hyper-AF ring, which correlates with the presence of the EZ band on OCT, suggesting that this demarcates the transition between healthy and degenerated retina. An important criterion for gene therapy is the preservation of intact photoreceptors in order to provide successful gene delivery. We measured the retinal sensitivity using microperimetry, and showed that despite macular atrophy, some residual sensitivity (i.e. remaining photoreceptors) may remain which can be targeted for therapy. However, we also noticed a limitation of microperimetry: greater variation in microperimetry results is found in patients with end-stage disease, which decreases the reliability of this testing method. Another psychophysical test is FST, which measures the sensitivity of the entire retina, and can be performed in all patients regardless of fixation capabilities, and even in those without measurable photoreceptor function on full-field ERG. A limitation of the FST is the inability to provide spatial information, as it can only give an indication of total photoreceptor function.

Our data supports the use of microperimetry and FST in clinical trials, as they provide complementary information on the residual visual function. This allows for the possible inclusion of patients in advanced stages of RP that were previously excluded based on non-detectable photoreceptor responses. Additionally, these tests can be used to measure treatment efficacy, allowing researchers to assess local and global improvements in visual function.

The knowledge on the retinal histopathology of patients with *RPGR*-IRDs is scarce. We obtained histopathology sections of a patient carrying an *RPGR* mutation with an advanced CRD/sector RP phenotype. Immunohistochemical analysis showed that in regions with degeneration of photoreceptors, reactive gliosis had taken place in the inner retina, also in regions without bone-spicule pigmentary changes. This process of reactive inner retinal gliosis may prove to be detrimental for treatments that require the use of the remaining neurons following the loss of photoreceptors, such as optogenetic strategies or retinal prostheses. Most therapies should therefore be applied at the earliest convenience for the best chance for successful therapy.

PHARC syndrome: a rare syndromic form of RP

In **Chapter 2.3**, we describe PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract) syndrome, a rare syndromic form of RP that is associated with neurological, audiological and ophthalmological manifestations. It is caused by variants in the *ABHD12* gene, which plays a key role in lipid metabolism. With only 50 cases described in the literature, PHARC syndrome is one of the rarest forms of RP, and much is still unknown about this disease entity. We describe that PHARC syndrome shows great clinical variability with respect to onset of disease and rate of progression. Because of the great clinical variability in presentation, many other diagnoses may precede before establishing PHARC syndrome.

From an ophthalmic perspective, patients do not exhibit the clinical hallmarks of RP (bone-spicule hyperpigmentation, optic disc pallor and vessel attenuation), but the fundus findings resemble an atypical variant of RP without hyperpigmentation. The presence of panretinal rod-cone degeneration could be established using ffERG, highlighting the importance of electrophysiological testing for this disease. Multimodal imaging showed loss of the outer retina similar as seen in non-syndromic RP. Another important finding is the presence of cataract in PHARC syndrome, between the 2nd and 4th decade of life. Interestingly, in some patients, cataracts were star-shaped and delineated the crystalline sutures of the lens, suggesting a congenital component.

The complexity of PHARC syndrome and the rarity of this disease make it a difficult diagnosis to establish. Genetic testing is necessary to confirm the presence of variants associated with *ABHD12*, but these tests may not be available in all hospitals. A multidisciplinary approach involving specialists from multiple different fields is

necessary to obtain a timely diagnosis of PHARC syndrome. An accurate diagnosis and a better understanding of the pathophysiological mechanisms in PHARC syndrome will facilitate the development of therapeutic strategies.

CRB1-associated IRDs: paving the path towards gene therapy

Proof of concept for gene therapy for *CRB1*-associated IRDs has been achieved in murine and human iPSC-derived retinal organoid models, with possibility of clinical gene therapy trials in the future. However, before making the translation to clinical studies, many knowledge gaps need to be addressed first, for example the natural course and identification of the most sensitive potential outcome measures.

In **Chapter 2.4**, we describe the first prospective natural history study in patients with *CRB1*-associated IRDs. Variants in *CRB1* causes a variety of phenotypes including early-onset RP, LCA, CRD and macular dystrophy. Many patients with C*RB1*-associated IRDs are affected at a young age, with progressive loss of visual function. In our 2-year investigation, we demonstrate that conventional parameters, such as BCVA and visual fields, remain relatively stable over time. However, microperimetry showed significant decline of retinal sensitivity over 2 years, thus preceding BCVA and VF, suggesting that this outcome measure might be appropriate to monitor efficacy for clinical trials. Also, FST was able to measure residual photoreceptor function in this cohort, which is beneficial in patients with *CRB1*-associated IRDs as ffERG responses are typically minimal or non-detectable.

We observed great variability in visual acuity, visual fields, and microperimetry; most likely due to nystagmus, severe loss of visual acuity and poor fixation capabilities. In future studies, it is important that the amount of variability is investigated, as this will inform us whether changes in outcome parameters are due to disease progression, treatment effect, or to test-retest variability in patients.

CLINICAL MANAGEMENT OF RP

Management of RP-associated complications

In the majority of patients, clinical management of RP remains symptomatic and is not curative in nature. There are several complications commonly found in association with RP, which should be closely monitored, and, if possible, managed timely to minimize their impact. Below, we list several common and uncommon complications associated with RP, their potential impact on RP and suggested treatment options.

Cataract

Cataract is a common anterior segment complication in RP patients.[5-8] Cataract associated with RP is present at a younger age than those with age-related cataract,

and most commonly is posterior subcapsular cataract (PSC), suggesting differences in the etiology of cataract formation between these two groups.[6, 7, 9] Previous studies have demonstrated that increased levels of pro-inflammatory cytokines and chemokines are present in the aqueous humor and vitreous fluid of patients with RP compared to the controls.[9, 10] These increased inflammatory levels were mainly observed in younger patients and in those with significantly lower visual function, suggesting that a pro-inflammatory environment may play an important role in cataractogenesis in RP.[9]

Significant cataract impairs visual function and additionally causes visual disturbances that may exacerbate existing functional symptoms in patients with RP.[11-13] The type of visual disturbances varies with the morphology of the lens opacity and includes symptoms of glare, photophobia and decreased contrast sensitivity, among others.[11] Straylight effects caused by cataract can aggravate visual disability.[14, 15] Considering the impact of cataract in patients with RP, surgical removal of the lens opacity can be offered to improve visual function and to relieve any functional symptoms. Currently, the most used surgery technique for cataract removal is phacoemulsification of the natural lens and implantation of an artificial intraocular lens (IOL).[16, 17] In the absence of other (ocular) comorbidities, cataract surgery leads to significant improvements in visual function. However, in patients with RP, visual prognosis is less certain as the cause of progressive vision loss can be caused by the increased clouding of the lens, by the ongoing retinal degeneration by RP or a combination thereof. Patients with RP are also at increased risk for intra- and postoperative complications, including intraoperative phototoxic damage to the retina, (increase in existing) CME and zonular dialysis, among others.[18-23] Furthermore, higher rates of posterior capsular opacification and anterior capsule phimosis have been described following cataract surgery in patients with RP, which may also negatively influence visual outcomes if left untreated.[24]

In our study (**Chapter 3.1.**), we also demonstrated significant visual improvements in the majority of patients with RP following cataract surgery. Patients with lower baseline BCVA had higher odds of achieving marked BCVA improvements (> 15 ETDRS letter gain). A possible explanation is that patients with poor preoperative BCVA have more extensive, vision-impairing cataract that allows for higher BCVA gains. Also, patients with preserved preoperative BCVA are limited by a ceiling effect. Previous studies on cataract surgery in RP have reported similar findings (Table 1).[7, 24-33]

Table 1. Overview of studies on cataract surgeries in patients with retinitis pigmentosa.

Study	Pts	Eyes	Follow-up	Baseline BCVA	Postoperative BCVA	BCVA change	Complications
Jackson et al. 2001	89	142	32.7 months	1.05 ± 0.38 logMAR	0.63 ± 0.49 logMAR	-0.42 logMAR	PCO (63%), CME (14%), CCS (10%)
Dikopf et al. 2013	47	80	23.3 months	1.23 ± 0.99 logMAR	0.81 ± 0.87 logMAR	-0.42 logMAR	PCO (83%), IOL dislocation (3%)
Bayyoud et al. 2013	52	46	26.0 months	1.45 ± 0.85 logMAR	1.32 ± 0.95 logMAR	-0.13 logMAR	PCO (44%), CME (4%), CCS (4%)
Garcia-Martin et al. 2013	35	35	1.0 month	0.10 ± 0.23 Snellen	0.48 ± 0.21 Snellen	0.38 Snellen	N/A
Nakamura et al. 2015	43	58	3.0 months	0.81 ± 0.51 logMAR	0.34 ± 0.43 logMAR	-0.47 logMAR	None
Yoshida et al. 2015	40	56	37.5 ± 22.6 months	0.76 ± 0.65 logMAR	0.45 ± 0.53 logMAR	-0.31 logMAR	PCO (84%), CCS (23%)
Davies et al. 2017	18	30	3.7 ± 3.3 months	1.09 ± 0.69 logMAR	0.61 ± 0.45 logMAR	-0.47 logMAR	CME (13.3%), PCO (66.7%)
Chan et al. 2017	42	67	6.9 ± 4.4 years	1.27 ± 0.42 logMAR	1.18 ± 0.49 logMAR	-0.09 logMAR	N/A
De Rojas et al. 2017	19	19	259 days	0.33 ± 0.20 logMAR	0.19 ± 0.17 logMAR	-0.14 logMAR	CME (32%), PCO (95%)
Lu et al. 2017	52	101	5.09 ± 2.2 months	0.12 ± 0.09 Snellen	0.21 ± 0.16 Snellen	0.09 Snellen	CCS (2%), increased IOP (2%)
Mao et al. 2018	70	109	3 months	0.80 ± 0.59 logMAR	0.45 ± 0.41 logMAR	-0.35 logMAR	N/A
Chatterjee et al. 2021	103	132	13.5 ± 25.1 months	1.21 ± 0.87 logMAR	0.66 ± 0.64 logMAR	-0.55 logMAR	PCO (17%), CME (5%), zonulolysis (3%). PCR (2%), uveitis (4%)
Chen et al. 2021	63	84	6 months	1.3 ± 0.7 logMAR	0.91 ± 0.88 logMAR	-0.39 logMAR	CCS (5%)
Miura et al. 2021	62	62	3 months	0.45 ± 0.25 logMAR	0.11 ± 0.19 logMAR	-0.33 logMAR	None
Nakamura et al. 2022	64	96	5.8 ± 2.4 years	0.64 ± 0.52 logMAR	0.61 ± 0.52 logMAR	-0.03 logMAR	PCO (53%), CME (3%), ERM (2%), macular hole (1%), VMT (1%)
Nguyen et al. 2022	225	295	0.8 ± 1.6 years	1.03 ± 0.79 logMAR	0.81 ± 0.87 logMAR	-0.22 logMAR	PCO (38%), CME (5%), zonulolysis (5%), CCS (2%), IOL dislocation (1%), PCR (<1%), endophthalmitis (<1%)

BCVA = best-corrected visual acuity; PCO = posterior capsule opacification; CME = cystoid macular edema; CCS = capsular contraction syndrome; IOP = intraocular pressure; N/A = not available; PCR = posterior capsule rupture; Pts = number of patients; ERM = epiretinal membrane; VMT = vitreomacular traction

Subjectively, visual improvement was reported between 44.8%-96.7% of patients included in these studies.[23] Possible predictors for visual outcomes suggested by previous studies include the integrity of the EZ and ELM in the fovea, and baseline BCVA.[34-36] Extensive loss of macular EZ integrity, often seen in patients with advanced

stages of RP, may cause irreversible vision loss, leading to no or only modest visual gains after cataract surgery.[25] Some authors have advocated the use of low-light settings during surgery and the use of blue-light filtering IOLs in an attempt to limit additional retinal phototoxicity, although the evidence to support these preventive measures in RP is very limited.[14, 37]

The presence of new CME or the exacerbation of existing CME, with reported rates of up to 32% (Table 1), can negatively influence the visual outcome, and chronic CME may even aggravate photoreceptor loss in patients and thus should be timely managed.[34] For patients with RP, a previous study recommended the simultaneous postoperative use of topical nonsteroidal anti-inflammatory drugs and CAIs for at least 3 months to prevent the risk of CME.[20] Alternatively, or in addition, parabulbar steroids may be administered at the end of the operation in an attempt to reduce the likelihood of postoperative (increase in) CME. SD-OCT imaging in the pre- and postoperative care of patients with RP-associated cataracts is useful for monitoring CME.

Incidence rates of up to 13% of zonular dialysis following surgery have been reported. This increased risk of zonular dialysis is believed to be caused by a low-grade intraocular inflammation process in RP that causes weakened zonular attachments.[19] During preoperative intake, signs of zonular weakness can be present, including phacodonesis and lens subluxation, indicative of moderate to severe zonular weakness. However, zonular weakness is best observed while maneuvering the nucleus intraoperatively. Surgeons should avoid unnecessary manipulation and strain on the lens zonules, by using optimal hydrodissection and bimanual rotation of the nucleus. Large capsulorrhexis can assist with optimal maneuvering, while also reducing the risk of capsular phimosis. The use of a capsular tension ring may also provide stability and decrease the risk of IOL (sub)luxation and anterior capsular phimosis, although the insertion itself of the capsular tension ring may also cause strain on the lens zonule system, so prophylactic insertion of such a ring may not be indicated.[23, 28] IOL (sub) luxation at short- or long-term follow-up in RP has been reported in several case studies and these cases were managed using scleral suture fixation or by replacing them with a range of anterior chamber IOLs after the (sub)luxated IOL had been removed, often requiring accompanying vitrectomy.[38-40]

Posterior capsular opacification is another common complication after cataract surgery and is believed to develop faster in patients with RP, with a significant posterior capsular opacification occurring after a median time of 12-15 months postoperatively, reported by two studies.[19, 24] It may already be pre-existent because of the presence of residual posterior capsular cataract remnants at the end of the cataract surgery. Posterior capsular opacification can be treated with neodymium-doped-yttrium-aluminum-garner laser capsulotomy, preferably using low energy levels, considering that this procedure can also induce CME.[41]

In summary, the current literature suggests that cataract surgery is beneficial for a large group of patients with RP, provided that there is a good preoperative diagnostic evaluation, with postoperative improvements in both objective and subjective visual outcome measures.[23] Ophthalmologists are advised to employ SD-OCT imaging pre- and postoperatively to evaluate EZ integrity and CME, and to be aware of signs of zonular weakness. Patients should be counseled about the increased risk of complications and the guarded visual prognosis following surgery in order to set realistic expectations.

Cystoid Macular Edema

The presence of CME has been variably reported, with prevalence rates from 10% to up to 70% in at least one eye between different study populations.[42-44] While CME can occur in every genetic subtype of RP, it is more commonly found in patients with adRP.[45] Significant CME in RP may cause reduction in visual acuity, and if left untreated, it might cause further degenerative changes in the retina, including macular hole formation.[46] However, the short-term and long-term additional visual impact and detrimental influence of CME in RP has not been firmly established.[43] The advent of OCT imaging in clinical practice has made the detection of CME more efficient, allowing for earlier diagnosis and treatment. It should be noted that cystoid changes in patients with RP are not necessarily consistent with active fluid leakage and CME.[47-52]

The specific pathophysiology of RP-CME remains to be elucidated, but multiple mechanisms have been proposed: leakage of fluid through the RPE due to insufficient RPE pumping fluid function; vitreomacular traction; breakdown of the blood retina barrier; Müller cell dysfunction; and antiretinal antibodies.[42, 43] Previous studies demonstrated that RP-CME typically resides within the inner nuclear layers (INLs) of the retina and does not cause significant disruption of the vascular plexus.[53, 54] These findings support the hypothesis that RP-CME is more likely to be related to Müller cell dysfunction, rather than being vasculogenic, although other possible underlying mechanisms cannot be excluded to date. In the case of postoperative occurrence of CME, which occurs in up to 20% of RP patients after cataract extraction, there may be a more important role for a vasculogenic factor and active leakage.[5, 18, 34]

Because the pathophysiology is not completely understood and different gene mutations are associated with different likelihoods of RP-CME, the appropriate treatment remains a subject of debate.[55-58] An in-depth review by Bakthavatchalam and colleagues on the treatment of RP-CME suggested that the oral carbonic anhydrase inhibitor (CAI) acetazolamide is an effective first-line treatment.[44, 57-60] The exact mechanism of CAIs on RP-CME remains to be elucidated, but it has been postulated that CAIs selectively inhibit different carbonic anhydrase isozymes located in RPE cells, improving the polarity of RPE cells and improving fluid transport.[61, 62] Several relatively small prospective and retrospective studies showed that oral intake of acetazolamide

causes a significant reduction in central macular thickness in up to 80% of patients with CME.[58, 60, 63] While CAIs may restore retinal structure, its effect on retinal function, i.e., visual acuity, appears to be limited, and the long-term functional and anatomical benefit of reducing CME in RP remains to be observed.[42, 44, 57, 60, 62, 64] In addition, there is a range of potential adverse effects of systemic CAIs, including paresthesia, malaise, nausea, altered taste, depression and drowsiness, as well as potential serum biochemical changes, including decreased serum potassium and increased chloride levels, thus discouraging prolonged use of CAIs.[65, 66] In rare cases, patients also develop renal stones as a consequence of prolonged CAI use.[67, 68]

As an alternative to systemic CAIs, topical CAIs such as dorzolamide and brinzolamide can be used for the treatment of CME. Previous studies have shown a significant decrease in CME in 30-81% of study eyes following the use of topical CAIs, although the efficacy of systemic CAIs in reducing CME was higher than that of topical medication.[44, 57, 63, 69, 70] Topical CAIs can be prescribed if patients experience any adverse effect from systemic medication. Despite the significant reduction in CME, re-occurrence of CME after a period of discontinued use of CAIs is common.[44, 63, 69-74] Therefore, patients need to be actively monitored for recurrent CME, which requires restarting CAIs.

Furthermore, intravitreal injections with anti-vascular endothelial growth factor (anti-VEGF) have also been proposed as treatment for RP-CME.[42, 75] Vascular endothelial growth factor (VEGF) is a protein important for angiogenesis, as well as for vasculogenesis.[76, 77] Thus far, given the limited evidence of efficacy as well as the patient burden, there is no indication for anti-VEGF treatment for uncomplicated RP-CME.

Intravitreal injection of a dexamethasone implant has also been used for the treatment of RP-CME. A prospective study by Veritti and colleagues compared the efficacy of dexamethasone implants versus oral acetazolamide (30 eyes in each arm), demonstrating that dexamethasone implants caused more reduction in central macular thickness and a higher BCVA letter gain compared to oral acetazolamide.[78] While the use of dexamethasone implants for RP-CME may be promising, current evidence on its usage and long-term effects in RP-CME is limited.[79-81] Furthermore, intravitreal injections of dexamethasone implants can cause increased intraocular pressure, cataract formation and subconjunctival hemorrhages, as well as more severe and rare complications such as retinal detachments, misplacement of the implant, and endophthalmitis.[82]

Based on the available literature, if there is an indication for the treatment of RP-CME, CAIs are currently the preferred choice, with systemic CAIs preferred over topical CAIs because of their comparatively superior efficacy, provided that the profile of side effects are acceptable for the patient. Oral acetazolamide can be prescribed when

there is significant central (fovea-involving) CME and patients should be informed of the common adverse effects, the possibility of refractory CME and the uncertainty regarding long-term benefit for visual function. More studies are needed on the long-term natural course of RP-CME, the use of anti-VEGF and steroid implants, the potential detrimental effect of cystoid fluid in the macula of RP patients and if treatment of CME has a short-term and long-term functional benefit.

Other Macular Abnormalities and Retinal Detachments

The prevalence of macular abnormalities, such as epiretinal membrane (ERM), macular hole and vitreomacular traction syndrome, has been estimated to be around 1.9% in patients with RP.[83] Significant epiretinal membranes cause visual disturbances (e.g., visual acuity loss, metamorphopsia and diplopia) and can also result in macular holes. The exact etiology behind epiretinal membrane formation remains unknown, although elevated inflammatory factors have been observed in the vitreous of patients with RP, suggesting that inflammation is likely a contributing factor.[84] Surgical outcomes for the treatment of the ERM in RP are limited; a study involving 10 RP patients that underwent pars plana vitrectomy and inner limiting membrane peeling for ERM showed improvements in retinal morphology for the majority of cases (82%), but no significant improvement in BCVA was observed.[85]

Similarly, the occurrence of macular holes is rare in RP and as a consequence, outcome rates of vitreoretinal surgery in patients with RP have only been reported in a select few case studies involving a small number of eyes.[46, 86-88] The study by Jin and colleagues showed an improvement in visual acuity and structural integrity of the retina following pars plana vitrectomy in three out of five treated eyes, as well as an improvement in the sealing of the macular hole. The remaining patient, who also had extensive retinal detachment, showed no change in visual acuity.[86] A different case report by Garcia-Fernandez and colleagues showed that primary surgery resulted in closure of the macular hole in the treated patient, but reopening of the hole occurred after two years.[88]

The prevalence of retinal detachments (RDs) in RP has been reported to be between 0.7% and 1.3%.[89-91] Retinal detachments occur at a relatively younger age in patients with RP than in those without RP. Retinal detachments are often rhegmatogenous in nature, although exudative and tractional forms have also been described.[89] In the study of Chan and colleagues, exudative RDs were mainly seen in patients with *CRB1*-associated IRDs.[89] In three previous studies, final reattachment rates between 86% and 96% were reported, using scleral buckling or vitrectomy, suggesting a favorable anatomical outcome.[89-91] An overview of surgical outcomes for retinal detachments in RP can be found in Supplemental Table S1.

Uveitis

Uveitis in patients with RP is relatively rare, with a prevalence estimated in one study at approximately 0.26%, although this is likely an underestimation as most patients have milder forms of uveitis and/or are asymptomatic.[92] Uveitis in RP most commonly presents as anterior uveitis, followed by intermediate uveitis and, even more rarely, as posterior uveitis.[92-95] Some forms of uveitis, such as acute zonal occult outer retinopathy and (atypical) advanced birdshot chorioretinopathy may mimic features of RP, such as pigment clumping and retinal vessel attenuation, which leads to initial misdiagnosis.[96, 97] A specific form of uveitis found in patients with RP is Fuchs' heterochromic uveitis, which has been reported in several case series.[98-104] The co-occurrence of uveitis in RP can be coincidental, but there may also be a role for underlying immunological abnormalities that play a role in the disease etiology of RP, which is supported by several animal and immunohistochemical studies.[95, 98, 105, 106]

Currently, there is limited evidence on the treatment of uveitis in RP. Only a few studies describe treatment modalities, and these case reports seem to show a low efficacy in preventing uveitis relapse.[94, 95] Majumder and colleagues have described the use of topical, periocular and oral corticosteroids for the treatment of 22 patients with anterior and/or intermediate uveitis, with varying results. Two patients with anterior uveitis developed CME, which was resolved using topical nonsteroidal anti-inflammatory drugs. The management of uveitis did not show improvements in visual acuity at follow-up.[92] While the treatment of uveitis does not necessarily improve visual function, monitoring the activity of inflammation remains important to prevent further complications that may worsen visual function such as CME formation, and leakage of the optic nerve and/or retinal vessels, findings which have all been described in patients with RP.[107-109]

Glaucoma

A common form of glaucoma found in RP is primary angle-closure glaucoma (PACG), with prevalence rates between 1.0% and 2.3%.[110-112] Previous studies have shown that the association between RP and PACG are related to nanophthalmos, short axial length, cataract and lens subluxation.[111] Anatomically, patients with a short axial length and/or cataract have a relatively shallow anterior chamber more prone to occlusion. Furthermore, the presence of zonular insufficiency and ectopia lentis in RP may cause forward displacement of the lens, which may also induce closing of the anterior chamber angle.[112] As PACG can cause irreversible optic nerve damage that may lead to further loss of remaining visual function in patients with RP, clinical work-up and timely intervention is crucial. In the acute setting, the overall goal for the management of PACG is to reduce intraocular pressure and to relieve angle closure. Glaucoma medications are given to lower intraocular pressure, to reduce pain and in preparation for laser peripheral iridotomy, which is the definitive treatment for PACG.

Fellow eyes should also prophylactically receive an iridotomy as they are also at risk for developing PACG.[113]

Rehabilitative and Psychological Management

The visual impairment caused by RP and the progressive nature of this disease may have detrimental effects on patients' general health, self-sufficiency and independence, which can profoundly impact their own quality of life and that of their caretakers.[114] The impact of RP is diverse and may result in physical, mental, emotional and social disabilities. The extent to which the lives of patients are affected by RP varies greatly between individuals and relies on several factors including their functional ability, age, daily activities, work, education, family, support networks and coping mechanisms.[114] Not all patients are aware of the rehabilitation services that can provide assistance for some of these aspects, and thus are left with unmet clinical needs.[114] Healthcare providers should screen patients for rehabilitation needs and, if desired, refer them to the appropriate services, such as low vision rehabilitation, psychological counseling and mobility training services, which are commonly present in visual rehabilitation centers. The aim of these services is to help patients manage the consequences of their disease and to lead a lifestyle as autonomous as possible, optimizing their quality of life.[115] Low-vision rehabilitation services (LVRSs) encompass a multidisciplinary team that aims to achieve the maximum potential of a patient's residual vision.[116, 117] The composition of this multidisciplinary team varies between different countries and may include, but is not limited to ophthalmologists, optometrists, occupational therapists, social workers and psychologists.[115, 118] Multiple studies have demonstrated improvements in the quality of life in patients with visual impairment following LVRSs.[119, 120] Rehabilitation services are tailored to a patient's individual situation, which are based on a patient's current visual abilities and their own rehabilitation goals.[121] Several instruments exist that can be used at the intake to screen for important rehabilitation needs, and to measure the efficacy of rehabilitation services. Common tools used at initial assessment within LVRSs may include variations of the National Eye Institute Visual Function Questionnaire, an instrument to measure vision-related quality of life, as well as the Activity Inventory, which systematically assesses the most important life domains and specific tasks for a patient.[121-123] A limitation of these aforementioned questionnaires is that they are not tailored to patients with RP, who may experience different difficulties than those, for example, with glaucoma. New questionnaires are being developed specifically for patients with IRDs in light of new upcoming therapies as a subjective outcome measure, such as the Michigan Retinal Degeneration Questionnaire.[124]

Without rehabilitation, patients with visual impairment may have to abandon tasks, for instance, those that require detailed vision, such as reading.[125] A low-vision aid (LVA) yields improvement in visual performance and encompasses corrective glasses; filtering lenses; optical and non-optical LVAs (e.g., magnifiers, telescopes, reading

stands); electronic assistive technologies, such as closed-circuit television, screen readers; and, more recently, portable electronic devices (e.g., Orcam or eSight).[126-128]

In **Chapter 3.2**, we explore impact of one electronic assistive device, the OrCam MyEye 2.0, on the quality of life in patients with IRDs. The OrCam is a wearable assistive technology device that utilizes artificial intelligence and computer vision to assist individuals with visual impairments. The device consists of a small camera mounted on a pair of glasses that can identify and read text, recognize faces, and provide audio descriptions of objects and environments. The OrCam is designed to enhance the independence and quality of life of individuals with visual impairments by providing them with additional visual information.

As visual function gradually becomes less in patients with IRDs, so does their ability to do their daily activities independently, and in turn their quality of life. In our study of 19 patients with advanced IRDs, we noticed that important rehabilitations goals were mobility indoors for patients with RP, and reading and administration for patients with cone-based dystrophies, which corresponds with the affected photoreceptors in each of these diseases. Following OrCam usage, we observed a significant increase in near reading abilities, as measured on 3 different questionnaires (NEI-VFQ, D-AI and the OFQ). Other subdomains or rehabilitation goals, remains unchanged after the test period of 5.2 weeks. These findings suggested that devices such as the OrCam can be particularly useful for improving reading abilities in patients with advanced IRDs, and less so for other activities. Further improvements are needed to improve the serviceability of the OrCam and similar devices to a broader audience. Several upgrades in the hardware and software of the OrCam have already been made to address these limitations.

The efficacy of LVAs is demonstrated by improvements in reading speed and acuity in clinical studies, although knowledge on other important factors such as the subjective preference and cost of LVAs, can also play an considerable role in the recommendation of these devices.[125] Simple adaptations can also be made at home, at school or at work to improve autonomous function and to create a safe environment.[129] Examples of these adjustments include improving lighting control, removing trip hazards, and creating contrasts between objects for easier identification.

Blindness is often ranked as one of the worst medical conditions by the general population among other very severe diseases, as well as being considered the medical condition with the highest impact on day-to-day life.[130] Nevertheless, the psychological consequences may be under-recognized. Loss of vision has been associated with depression, social isolation, sadness, anxiety and fear.[131-133] Few studies have investigated the psychological impact of LVRSs which showed improvements in mental well-being following rehabilitation.[134] Further studies are needed to understand

the effectiveness of LVRSs on mental health and whether the implementation of psychological interventions such as cognitive behavioral therapy, should be routinely embedded in LVRSs.[135]

The ongoing degeneration of the retina due to RP causes progressive loss of visual function, which can have a significant impact on a person's daily life, the ability to perform tasks, and emotional well-being. While objective outcome parameters measure a patient's visual function, they do not necessarily reflect a patient's own experience, for which subjective outcome measures are more appropriate.

In **Chapter 3.3**, we explore the longitudinal changes in patients with *CRB1*-associated IRDs over the course of 4 years using the most commonly ophthalmic patient reported outcome measure to date, the NEI-VFQ. While praised for its simplicity, the NEI-VFQ in its classical test theory form does not meet the current standard for psychometric testing due to lack of unidimensionality and poor item fitting. In our study, we employed the use of Rasch analysis to tackle some of the limitations, and we made use of previous item measure calibrations to analyze the quality of life in this cohort. When looking at objective outcome measures, we observed a decline in BCVA and microperimetry over the course of 4 years. For subjective measures, we observed a decline in the 'visual function' domain over 2 years, but not over 4 years. These findings illustrate that changes in objective visual function do not necessarily reflect a patient's experience. By including both subjective and objective outcome measures, a more complete and nuanced assessment of treatment effectiveness can be achieved. For subjective outcome measures, the NEI-VFQ can be relevant and meaningful for the design of future clinical trials. New questionnaires such as the Michigan Retinal Degeneration Questionnaire, are also being developed that meet current psychometric standards.

For individuals with extensive visual field loss such as in RP, traveling independently can become increasingly difficult, especially in unfamiliar and poorly lit environments.[136] Many aspects of life are impeded by the inability to travel, such as social interaction and work; therefore, mobility impairment may also significantly impact an individual's quality of life. In such cases, orientation and mobility training can be useful, which aims to teach patients to ambulate (un)known environments safely and independently. Examples of mobility training objectives include training on the use of a white cane when using public transport, riding a bike and using navigation devices while traveling.[137]

LVRSs should be an integral part of the care for eye diseases, especially in patients with significant visual impairment, such as those caused by RP, to improve their independence and overall well-being. It is advisable to refer patients to LVRSs when unmet needs are evident as well as when these needs are not so apparent, as low-

vision centers provide many helpful services that are not necessarily known to a patient.

Investigational Treatment Modalities

Improved understanding of the underlying mechanisms of RP has driven current research, resulting in the dawn of novel treatment strategies. The timing and underlying mechanism causing retinal degeneration determines a patient's eligibility for treatment. Below, we briefly explain the key features of current and emerging treatment modalities, their relevance in the treatment of RP and IRDs and their advantages and limitations.

Gene-Dependent Strategies

Ocular genetic therapies have become an emerging treatment modality for a wide variety of IRDs and have been successfully used in mice, dogs and now clinically in patients.[138-140] Retinal diseases appear to be excellent targets for gene-based therapies as the eye is highly compartmentalized, immune privileged, and are relatively accessible for local administration, while there is an elaborate armamentarium of structural and functional tests to evaluate treatment efficacy. Gene-based strategies are most effective in the early stages of disease, as they aim to prevent further degeneration of the surviving target cells, whereas they are unable to restore cells that have already degenerated.[141] The term gene therapy encompasses different strategies based on the transfer and application to different nucleic acids.

Gene Augmentation Therapy

The most straightforward strategy is gene augmentation therapy, in which a wild-type (normal) copy of the mutant gene is delivered to the site of interest with the use of a vector in which the correct gene is packaged for delivery at the target cells. The vector that is generally used is an adeno-associated virus (AAV), which has been extensively researched, has high transduction efficiency and exhibits relatively low immunogenicity.[142] However, other viral and non-viral vectors are also studied, and each has its advantages and disadvantages.[143] The correct copy of the gene carried by the vector aims to compensate for the disease by restoring wild-type expression, thus preventing further disease. This method can be particularly useful for autosomal recessive and X-linked RP as these variants typically result in loss-of-function. In contrast, adRP may result in gain of function or dominant-negative variants, which may require alternative approaches, such as gene silencing or knockdown-and-replacements strategies.[144] In patients with *RPE65*-associated IRDs, subretinal administration of functional copies of *RPE65* using an adeno-associated virus vector resulted in functional improvements (e.g., BCVA, FST blue, and multi-luminance mobility test).[139, 145-148] A meta-analysis revealed that changes in BCVA were significant at 1 year after treatment, but afterwards declined to baseline BCVA 2-3 years post-treatment. It is possible that photoreceptors continue to degenerate due to

insufficient delivery of functional genes, or that photoreceptors had already reached a pre-apoptotic state at the moment of therapeutic intervention.[149] A recent review demonstrated that the treatment effects of *RPE65*-gene therapy lasts up to 7.5 years after administration, which suggests that multiple gene therapy doses are needed to provide clinical stability during a patient's lifetime.[150] A single dose of FDA-approved Luxturna costs approximately USD 425,000 per eye per treatment. Furthermore, a subset of *RPE65* patients developed chorioretinal atrophy as a side effect of the subretinal administration of gene therapy.[151, 152]

The challenges in gene augmentation strategies lie in the fact that it is a gene-specific therapy and thus cannot be universally applied for all IRDs. Each gene in RP varies in its clinical course, affected cell types and size, among other factors. Therefore, each gene may differ in its optimal timing for therapeutic intervention, the method of administration and its therapeutic delivery. While subretinal delivery has a more direct effect on photoreceptor cells, it provides treatment only for a limited region of the retina, thus requiring multiple or larger treatment zones for better outcomes.[153] Furthermore, intravitreal and subretinal delivery can induce immune and inflammatory responses which can typically be managed with steroid therapy, but in rare cases may result in significant ocular inflammation with sight-threatening complications.[154] For many large genes in RP, such as *USH2A, ABCA4* and *EYS*, AAV vectors cannot be used as a vehicle considering the limited packaging capacity of approximately 4.7 Kb.[145, 155] Different viral vectors have been suggested, which differ in their gene-carrying capacity, cellular tropism, immunogenicity and mutagenicity.[140] Aside from *RPE65*, a range of RP-associated genes are currently targeted in gene-therapy trials, including but not limited to *RPGR, GUCY2D, XLRS* and *CRB1*.[140, 149]

CRISPR/Cas9-Based Therapy

Gene editing strategies, such as repurposing the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 system, have recently emerged as a potential solution for the limitations brought by gene augmentation strategies.[145, 149, 156-158] In CRISPR-Cas9 gene therapy, a Cas9 endonuclease is delivered to the target region via guide RNA, which causes double-strand breaks in the predefined regions of the genome. Subsequently, DNA-repair mechanisms are activated, namely non-homologous end joining (NHEJ) or homology-directed repair (HDR). Based on these two repair mechanisms, several types of gene editing can be performed. Using NHEJ, the ends of the cleaved DNA are ligated with or without the addition of base pairs, often resulting in gene inactivation. If multiple guide RNAs are introduced that target separates sites, NHEJ can be used to delete specific sequences. If a DNA template homologous to the target region is introduced alongside the CRISPR-Cas9 system, cells can even correct a gene, or insert a new gene using HDR mechanisms.[156]

As with any form of gene therapy, the main challenges of CRISPR-Cas9 include the delivery of the CRISPR-Cas9 complex, and the potential risk of an immune response. In addition, a major drawback for the use of CRISPR-Cas9 therapies are potential off-target effects. When using the CRISPR-Cas9 system, the guide RNA may target different regions than intended due to similarities within the genome, subsequently resulting in unwanted genomic modifications.[159] Furthermore, HDR efficiency, which is required to correct IRD-causing variants, in retinal cells is low. HDR functions mainly in dividing cells and is not highly efficient in post-mitotic retinal cells.[157]

Antisense Oligonucleotide Therapy
RNA therapies, such as antisense oligonucleotides (AONs), are an interesting treatment modality for IRDs, as they provide a possible solution for some patients with genetic variants not suited for AAV-gene therapy, e.g., patients with splice-site defects.[160, 161] AONs are short chains of nucleic acids that bind to a specific complementary messenger RNA (mRNA) to modify the expression of a given nucleotide sequence. The exact working mechanism differs between AONs, as they can be used for example, to correct pre-mRNA splicing, for exon skipping or for mRNA knockdown.[149]

There are some potential advantages of AONs over DNA-based therapies: AONs are relatively small in size and can fit current vectors; they do not directly modify DNA; and they do not induce double-strand breaks, thus not interfering with the endogenous expression of the target gene.[162] A limitation is that AONs have a limited duration effect based on their half-life and multiple intravitreal injections over the course of disease are likely needed.[161] Currently, no approved RNA therapies are available for IRDs and more data are needed to support the efficacy in this group of diseases.[161]

Gene-independent strategies

Optogenetics
In late-stage RP, degeneration of photoreceptors may reach a point in which the window of therapeutic opportunity for ocular genetic therapies is surpassed. The remaining neurons, such as dormant cones, bipolar and retinal ganglion cells, are typically preserved until end-stage disease, making them possible targets for optogenetic therapies.

The key idea of optogenetic therapy is to deliver and express genetically encoded light-sensitive proteins called opsins to the remaining light-insensitive neurons in the inner retina of patients with RP via viral vectors.[163] Once opsins are expressed in these target cells, they can be stimulated by light and invoke a visual response, thus bypassing lost or damaged photoreceptors. If the targeted cells are connected to other cell types in the retinal circuit, light also modulates the activity of these cells.

Optogenetic therapy can theoretically be applied to all patients with end-stage RP, regardless of genotype.[164]

Several human clinical trials are ongoing that involve optogenetic therapy in patients with RP (NCT02556736, NCT03326336, NCT04919473, and NCT04278131). Different types of opsins have been used; however, all studies use an AAV2 or similar variant as a viral vector via intravitreal injections, targeting retinal ganglion or bipolar cells. In the study by Sahel and colleagues, partial recovery of visual function was observed in a patient with light perception vision that received the AAV vector containing the light-sensitive protein ChrimsonR. With light stimulation via engineered goggles, the patient was able to locate and perceive different objects in a controlled environment, demonstrating proof-of-concept for the use of optogenetic therapy in RP, although further optimization is likely needed.[165]

Stem cell therapy

Stem cell therapy involves the use of stem cells to replace or repair cells in the retina and can be applied in patients with end-stage RP regardless of genotype.[157] The treatment can be categorized by effect, i.e., replacement or preservation of cells, and stem cell type as follows: embryonic stem cells (ESCs); induced pluripotent stem cells (iPSCs); hematopoietic stem cells; mesenchymal stem cells (MSCs); and retinal progenitor cells (RPCs).[166-172] Stem cells with a higher cell potency, such as pluripotent ESCs and iPSCs, come with more extensive differentiation properties and can be used for the replacement of retinal cells.[166] These cells, as well as their derivatives, have a higher risk of tumorigenesis and uncontrollable cell migration when compared to lower-cell-potency stem cells.[166, 173] The tumorigenesis of a treatment dose is closely monitored before administrating it to a patient, but no extensive long-term data are currently available.[166] RPCs can be derived from ESCs, iPSCs and MSCs, among others. These cells show promising results with increased BCVA outcomes in injected eyes, but are relatively self-limiting regarding expansion compared to pluripotent cell lines. [174, 175] RPCs also retain their capacity to differentiate in preclinical studies, which poses challenges post-transplantation.[166, 174, 176] MSCs, with their lower cell potency, are considered safer and have more long-term data on the risk of tumorigenesis. Patients treated with bone-marrow-derived MSCs showed initial improvements in BCVA, although their vision reverted to baseline at 12-month follow-up.[168, 169] Stem cell therapy is still in the early stages of development, and further research is needed to refine and optimize its technique and to determine its safety and effectiveness in the treatment of IRDs. Important hurdles of stem cell therapy include potential immune rejection, tumorigenicity and surgical complications.[176] Nevertheless, it can be a promising treatment option for patients with end-stage retinal disease.[168, 177]

Retinal Prostheses

Electronic retinal implants are designed to provide a basic sense of visual function in severely visually impaired patients.[149] In essence, retinal prostheses stimulate remaining retinal neural cells with electrical pulses via an electrode array. This treatment is primarily intended for patients with little to no visual function as the current resolution of vision is low.[178] The number of electrodes, amount of stimulation and the remaining retinal function all play a role in the quality of perception created by retinal prostheses. Furthermore, patients require a relatively intact posterior visual pathway to ensure correct visual processing of light stimulation.[178] Retinal prostheses can be utilized via direct electrical stimulation, where an external processing unit (e.g., a digital camera mounted on eyeglasses) captures real-time images which are then transmitted to the retinal implant, or via photodiodes arrays, which are directly imbedded into the retinal space and convert projected light patterns into local electric currents.

Retinal implants can be installed in the epiretinal, subretinal or suprachoroidal space.[179, 180] In the epiretinal configuration, the implant is placed in the near vicinity and directly interacts with the retinal ganglion cells. In the subretinal configuration, the implant is positioned between the outer retinal layer and retinal pigment epithelium, at the site of the photoreceptors. The suprachoroidal approach was developed to prevent damage to the neural retina, as the stimulating electrode array is not directly attached to the retina. However, this meant that electrodes were placed further away from the intended cells, thus requiring higher currents for stimulation.[179, 181, 182]

Several retinal implants have been developed, of which three have been approved by regulatory authorities and implanted in over 500 patients over the past two decades as follows: The Argus II, developed by Second Sight Medical Products, which was an epiretinal implant with glasses paired to a processing unit; Retina Implant Alpha-AMS and the Retina Implant Alpha-IMS by Retina Implant AG, which used a subretinal electrode array. Up to 20/1260 Snellen vision was achieved using Argus II, and 20/546 Snellen was achieved with the Retinal Implant Alpha-AMS.[178]

The implants do not come without risks as up to 30-40% of Argus II users showed adverse events of conjunctival erosion, hypotony, conjunctival dehiscence or endophthalmitis within five months after implantation.[183, 184] Alpha-IMS (by Retina Implant AG) showed increased intraocular pressure caused by subretinal bleeding in 1 out of 19 patients (5.3%).[184] Retina Implant AG and Second Sight Medical Products, have withdrawn their current products, with the latter now testing a cortical visual prosthesis in an attempt to address a wider patient group.[178, 185]

Retinal protheses are intended for patients with limited visual function, although the visual benefit with current techniques appears modest. Future developments in retinal prostheses should focus on increasing resolution of vision, visual fields and to minimize

adverse effects as result of electrode array implantation, which require innovation from engineering, software and electrophysiological perspectives.

Neurotrophic Factors

Neurotrophic factors are proteins that promote the survival, differentiation and growth of neuronal cells. Several neurotrophic factors have been studied in animal models for the potential to treat retinitis pigmentosa, including ciliary neurotrophic, nerve growth, and brain-derived neurotrophic factors.[186] Improvements in scotopic and photopic responses were observed in eyes that received ciliary neurotrophic factor (CNTF) compared to control eyes. For clinical delivery, direct intravitreal or subretinal neurotrophic factor injections have been the most common route.[186] However, an implantable device has also been suggested as it allows for the long-term release of neurotrophic factors, minimizing the risk accompanied by repeated injections. Several clinical trials have been conducted to evaluate the safety and effectiveness of CNTF as a treatment for retinitis pigmentosa. In one phase 1/2 clinical trial, CNTF was administered to patients with retinitis pigmentosa via a slow-release implant in the eye. The results of this trial showed that CNTF was generally well-tolerated and may have some beneficial effects on visual function in patients with retinitis pigmentosa.[186] Further randomized clinical trials evaluated the use of encapsulated-cell-ciliary neurotrophic factor implants for RP, showing no significant improvements in BCVA and visual field sensitivity for patients in the short (12 months) or long term (60–96 months).[187, 188]

Neuroprotective Agents

In rod-specific retinal diseases, cone photoreceptors may still degenerate.[189] It is hypothesized that when large amounts of rods degenerate in RP, oxygen consumption in the retina is severely reduced, leading to the generation of large amounts of toxic free radicals.[189] These compounds are harmful to the remaining cone photoreceptors.[2] Additionally, the production of rod-derived cone viability factor is also affected, making cone receptors more vulnerable to degeneration.[190, 191] N-acetylcysteine (NAC) and its more potent version, N-acetylcysteine amide (NACA), are powerful antioxidants that have shown to preserve cone function in animal models of RP.[3,4] In the FIGHT-RP1 study, the therapeutic benefit of daily intake of NAC was investigated, which showed improvements in visual function over the study period of 6 months.[192] These improvements diminished once patients discontinued the study medication. A retrospective study by the same group found similar neuroprotective features in the macula, as measured on microperimetry.[193] Another studied neuroprotective factor includes cerium oxide nanoparticles (CeO_2-NPs), which are nanocrystals with antioxidative effects derived from the rare earth element cerium.[194] In rat models, these have been shown to be effective in preserving photoreceptor function as well as slowing down the loss of photoreceptors.[194, 195] So far, human clinical trials in RP

patients have not been conducted. Currently, no neurotrophic drugs have been approved by the regulatory authorities.

Nutritional Therapies

Dietary supplements, such as vitamin A, lutein and docosahexaenoic acid (DHA) supplements, have been previously studied in patients with RP. Berson and colleagues published their study in 1993, where they assigned 601 non-genotyped RP-patients with either 15,000 IU/d vitamin A, 15,000 IU/d vitamin A plus 400 IU/d vitamin E, trace amounts of both vitamins or 400 IU/d vitamin E.[196] The first two groups showed a slower decline in retinal function based on full-field cone electroretinography compared to the latter two. This group conducted a follow-up study in 2004, assigning RP-patients with either DHA plus vitamin A (treatment group) or fatty acid plus vitamin A (control group), with a follow-up of two years. The authors concluded that the DHA + vitamin A group slowed the disease course of retinitis pigmentosa compared to patients in the group not assigned to DHA.[197] Similar effects of vitamin A supplements were also found in children by Berson and colleagues.[198] It has been postulated that because vitamin A is an important chromophore in the visual cycle, vitamin A supplementation can compensate for deficiencies in patients with RP.[199] Currently, less than 10% of the genes in RP involve genes associated with vitamin A metabolism.[200]

A randomized clinical trial by Hoffman and colleagues (DHAX trial) investigated the use of high dose DHA in patients with X-linked RP over the course of 4 years.[201] The results of this study demonstrated that DHA was not effective in slowing down rod or cone ERG progression. A second analysis of the DHAX trial revealed that DHA might reduce the rate of progression in final dark-adapted thresholds and visual field sensitivity parameters.[201, 202]

Recent reviews concluded that there was no clear benefit of vitamin A and/or DHA for patients with RP, in terms of mean change in visual fields or ERGs.[203-205] An editorial by Massof and colleagues concluded that there was no convincing evidence that vitamin A is beneficial, and may even carry potential health risks.[206] Excess vitamin A compromises liver function and may cause birth defects.[206] Furthermore, careful consideration should be given to the possibility that RP is caused by specific genetic variants (e.g., in the *ABCA4* gene), as it has been shown in animal models that an excess of vitamin A may boost the accumulation of lipofuscin in the retina and accelerate disease progression.[200, 207, 208]

Taken together, there is no strong evidence that supports the use of nutritional supplements for patients with RP. Nutritional supplements may slow down disease progression in IRDs closely tied to the vitamin A pathway in the retina (e.g., *LRAT*, *RPE65*, *RLBP1*, *RDH5* and *RDH11*), although its clear benefit has not yet been sufficiently proven in studies.[200] Vitamin A should be avoided in patients with genetic subtypes

susceptible for excess vitamin A (e.g., variants in *ABCA4*) as this may potentially accelerate disease progression.[209] Patients who do receive high doses of vitamin A should undergo laboratory work-up prior to therapy as longstanding use of vitamin A can result in toxicity (e.g., birth defects, liver failure, osteoporosis and central nervous system disorders).[210] For these reasons, most ophthalmologists do not prescribe nutritional supplements to patients with RP as routine care.

CONCLUDING REMARKS

The paradigm of IRDs has shifted from a diagnostic field to one in which potential curative treatments are being developed. For patients with RP who are eligible for current or upcoming clinical trials, establishing the natural history and defining clinical endpoints is essential to measure treatment efficacy. As genetic subtypes may display differences in clinical characteristics, natural progression and disease severity, outcome measures need to be tailored to each subtype of RP. Therefore, establishing the clinical and genetic diagnosis of patients with RP should be the first step, as many of the consecutive management steps rely on a thorough knowledge on the genetic and clinical characteristics (Figure 1). As RP is a rare disease, an international collaboration to facilitate retrospective and prospective studies is highly recommended. Modern outcome measures such as microperimetry and FST should be considered in future trials, as they provide additional insight into the remaining photoreceptor function. Upcoming studies should also investigate the test-retest variability of key measurement tools, as common problems in RP, such as severe visual impairment and nystagmus, can influence testing results.

The most common comorbidities, such as cataract and CME, can be managed using current treatment options. Patients with difficulties in daily activities due to reduced functional vision can be referred to low vision rehabilitation centers where they may obtain assistance in performing daily activities, which includes the prescription of low vision aids, in order to maintain independence. Validated patient-reported outcome measures are helpful in detecting rehabilitation needs, and to measure treatment effect from a patient's perspective. Developing a RP-specific questionnaire will be beneficial for obtaining the most relevant information and accurate information for managing this disease, which should be a focus for future studies.

Patients should not only be informed about new treatment modalities, but also about currently available clinical management possibilities outside curative treatment, as they may provide relief of physical, psychological and social burden until early therapeutic intervention and prevention are possible. With a range of future treatments on the horizon, the current management options should not be overlooked.

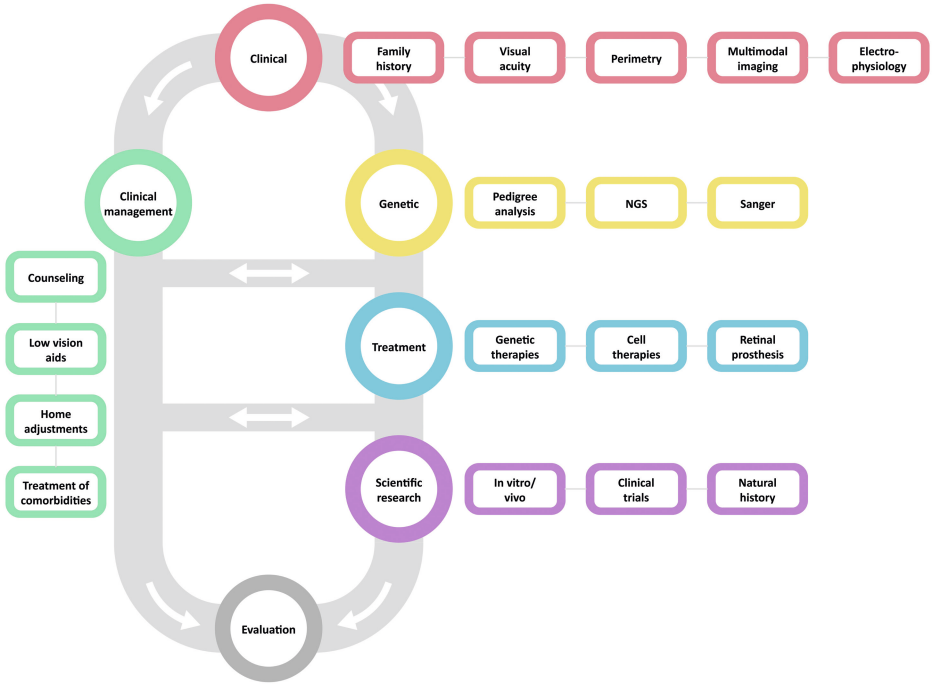

Figure 1. Flowchart demonstrating the clinical management of patients with retinitis pigmentosa (RP). The first step should be identifying patients with possible RP clinically, after which genetic testing should be performed, when available, if a diagnosis of presumed RP is made. Simultaneously, further clinical management should be offered through counseling, low-vision aids, home adjustments and treatment of comorbidities. Depending on the underlying causal gene, symptoms and severity of RP, treatment eligibility is assessed. Additionally, patients may opt to participate in ongoing research. The landscape for RP continues to change, and regular follow-up is advised to remain up to date with current clinical management and novel therapies.

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Supplemental Table S1. Overview of studies involving patients with retinitis pigmentosa that underwent surgery for retinal detachments.

	Chan et al. 2020	Dave et al. 2016	Rishi et al. 2018
Sample size	90 patients	17 patients	31 patients
Follow-up	15.4 years	8.52 ± 12.6	33 months (range 1-145)
Mean Age	Mean age 32.8 years	Mean age: 34.5 years	Mean age 22 years
Type of RD	Rhegmatogenous (68%) Exudative (21%) Tractional (3%) Combined (8%)	Rhegmatogenous (100%)	N/A
Intervention	Scleral buckling (3%) PPV (20%) Unknown surgical intervention (39%)* Conservative (28%) Not treated (10%)	Scleral buckling (30%) PPV (35%) Not treated (35%)	Scleral buckling (42%) PPV (32%) Not treated (26%)
Attachment rate	85%	91%	96%
Change in BCVA	1.52 vs 1.25 logMAR (p = 0.098)	1.4 ± 0.9 vs 1.1 ± 0.8 logMAR (p = 0.15)	1.63 ± 0.89 vs 0.87 ± 0.25 logMAR (p < 0.001)
Complications	Re-RD (n = 5) High IOP (n = 3) UGH (n = 1) Scleritis (n = 1) IOL subluxation (n = 1)	N/A	Re-RD (n = 3) Epiretinal membrane (n = 3) cataract (n = 2); Macular hole (n = 1); High IOP (n = 1)

*BCVA = best-corrected visual acuity; PPV = pars plana vitrectomy; IOP = intraocular pressure; UGH = uveitis-glaucoma-hyphaema syndrome; IOL = intraocular lens; RD = retinal detachment; re-RD = retinal re-detachment. *No information was available for the remaining surgical interventions in this study by Chan et al. Patients with exudative retinal detachments were treated conservatively. Patients that were not treated were due to poor visual prognosis.*