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Exploration of retinitis pigmentosa and the possible effects of therapy for individuals

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Thesis

EXPLORATION OF RETINITIS PIGMENTOSA AND THE POSSIBLE EFFECTS OF THERAPY FOR INDIVIDUALS

by

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FOR INDIVIDUALS

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ABSTRACT

Retinitis Pigmentosa (RP) is the leading cause of blindness in people under 60. This cluster of mutations affects about 1 in 4000 people in the United States of America (approximately 200,000 Americans) and 1 in 5000 in the entire world population (about 1,000,000 people worldwide). (O'Neal & Luther, 2024) The average age of onset of symptoms for RP is between 25 to 40, with a median age of 36.5. (Tsujikawa et al., 2008) However, there are cases where the patient can display symptoms before age 20 (as early as ten years old) or after age 65. RP is a cluster of mutations affecting proteins, which diminish or completely impair their function making them unable to transduce light to energy. This ultimately leads to decreased vision. Though RP explicitly causes the breakdown of the RPE and photoreceptors, this physiological description explains how RP can affect the overall vision of an individual. There are no cures for RP and few methods to reduce the onset of the disease such as dietary supplements, minimizing exposure to ultraviolet light, treating comorbid diseases such as cystic macular edema treatments, using visual aids, and undergoing surgery in late-stage RP. Though many promising treatments are being researched the

estimated period before these treatments are used in a practical clinical setting is unknown. Therefore, this paper proposes a therapy model that will address the four meta-themes to increase the quality of life of individuals with RP: (1) experience with the healthcare field and social support, (2) managing one's identity with RP, (3) living with the practical and emotional issues with RP, (4) and adaptive/maladaptive coping mechanisms. The model will begin with patients' interactions with physicians during diagnosis and enrollment into therapy. In the counseling portion, the paper will delve into managing identity and developing robust coping mechanisms, which, if worked on, could improve practical and emotional issues with RP.

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LIST OF ABBREVIATIONS

AAV	Adeno-associated Virus
Ad	Adenovirus
ADL	Activities of Daily Life
CBT	Cognitive Behavioral Therapy
CC	Connecting Cilium
cGMP	Cyclic Guanosine Monophosphate
CME	Cystoid Macular Edema
CNTF	Ciliary Neurotrophic Factors
DCP	Deep Capillary Plexus
ERG	Electroretinogram
EZ	Ellipsoid Zone
GPCR	G-protein Coupled Receptor
hiPSC	Human-Induced Pluripotent Stem Cells
IGF-1	Insulin-Like Growth Factor-1
IS	Inner Segment
LV	Lentiviruses
Meta II	Metarhodopsin II
MHC class II	Class II Major Histocompatibility Complex
miRNA	Micro- Ribonucleic Acid
mRNA	Messenger Ribonucleic Acid

OCT	Optical Coherence Tomography
OS	Outer Segment
RISC	RNA-induced Silencing Complex
RP	Retinis Pigmentosa
RPE	Retinal Pigmented Epithelium
SCP	Superficial Capillary Plexus
shRNA	Short Hairpin Ribonucleic Acid
siRNA	Small Interfering Ribonucleic Acid
VPU	Video Processing Unit

Introduction

Retinitis Pigmentosa (RP) is the leading cause of blindness and inherited blindness in people under 60. This cluster of mutations affects about 1 in 4000 people in the United States of America (approximately 200,000 Americans) and 1 in 5000 in the entire world population (about 1,000,000 people worldwide). (O'Neal & Luther, 2024) The average age of onset of symptoms for RP is between 25 to 40, with a median age of 36.5. (Tsujikawa et al., 2008) However, there are cases where the patient can display symptoms before age 20 (as early as ten years old) or after age 65. The term "retinitis" was given to the disease due to the inflammatory appearance of the retina; despite the name, RP's underlying pathogenesis is not inflammatory but the genetic degeneration of the retina. "Pigmentosa" is due to the peripheral pigmentary darkening seen during the fundus photo examination due to the retinal pigment epithelium and endocytic cells containing melanin moving into the retina. (Garg, 2022) One of the continuous struggles to find a treatment for RP is due to the incredibly heterogeneous nature of the disease, as 73 genes and over 3000 mutations in these genes have been identified to be linked to non-syndromic RP. Usher syndrome, a syndromic form of RP affecting hearing, has been linked to 15 genes, outside of the 73 genes associated with non-syndromic RP. Furthermore, Bardet-Biedl syndrome has been identified to be linked to 18 unique genes. (Daiger, 2024) Despite multiple manifestations of vision loss in RP, blindness is

due to the degeneration of photoreceptor cells, initially involving the rod cells and then cone cells during the later stages of RP.

The first part of this thesis will explain RP by first illustrating the anatomy, physiology, and histology of the eye. The next objective will be to create a foundational understanding of RP by explaining its etiology, diagnostic criteria, timeline pathophysiology, and current/future treatment options. Finally, the paper will evaluate four meta-themes associated with the quality of life of RP patients in hopes of finding a suitable therapy option to help provide a sense of independence and combat common mental illnesses associated with sensory loss.

Anatomy

The eye is an organ, a part of the visual system; it is a fluid-filled sac known as vitreous and aqueous humor, and three different layers of tissue encapsulate that. The outermost layer of the eyeball is the sclera, a white protective layer made of dense connective tissue; however, when over the lens of the eye, this layer takes on a transparent hue known as the cornea. The intermediate layer is divided into two distinct components: anterior, which includes the iris and ciliary bodies, and posterior, comprising the choroid. The iris is the pigmented membrane seen just behind the cornea, and the ciliary body sits just behind the iris, working as two opposing muscles that adjust the size of the pupil to light. The choroid is a well-vascularized layer of capillary beds between the retina and

sclera. The final layer is the retina, a sensory layer comprising the photoreceptor cells known as rods and cones. The two layers that RP generally affects are the retinal pigment epithelium (RPE), a layer that lies between the retina and choroid, and the retina. (figure 1)

The mutation that affects the RPE is associated with a specialized protein called RPE65. The RPE65 protein is related to converting a single photon into an electrical signal known as the visual cycle. The protein converts trans-retinyl esters to cis-retinol; therefore when RPE65 is nonfunctional it leads to an accumulation of trans-retinyl esters. However, there are varying effects as the mutation can differ from point, missense mutations, and even slight rearrangements. (Gu et al., 1997) Furthermore, RPE65 has been identified to be a part of the outer segment metabolism of the RPE layer. A mutation in RPE65 leads to an accumulation in the outer segment leading to toxicity; furthermore, the proximity of RPE to the rods and cones leads to the degeneration of the retina.

The eye's retina is filled with photoreceptors distinguished as rods and cones. Rods are much more sensitive to light as they are used to detect changes under dim lighting. Cones are more susceptible to high-intensity light and are used for visual acuity and color perception. Despite human vision being dominated in daylight, there are approximately 120 million rod cells and 9 million cone cells in the retina. Both rods and cone cells possess five compartmentalized structures:

(figure 2) outer segment (OS), connecting cilium (CC), inner segment (IS), nuclear region, and synaptic region. Other than varying functions, the structural differences between the OS are what distinguishes these two types of cells. (Goodwin et al., 2019) Rod cells possess a much longer OS with a cylindrical shape of stacked discs encapsulated in a plasma membrane. The cone cells possess a shorter OS with a cone shape with multiple evaginations along the OS. (Molday & Moritz, 2015) The OS is a part of the visual cycle, known explicitly as phototransduction, as it converts 11-cis-ral into atROL. The converted electrical signal then goes through the bipolar and ganglion cells, becoming the optic nerve. RP mutations generally affect the rods and, as symptoms progress, may affect the cones and RPE; however, some mutations can initially affect the cones and RPE.

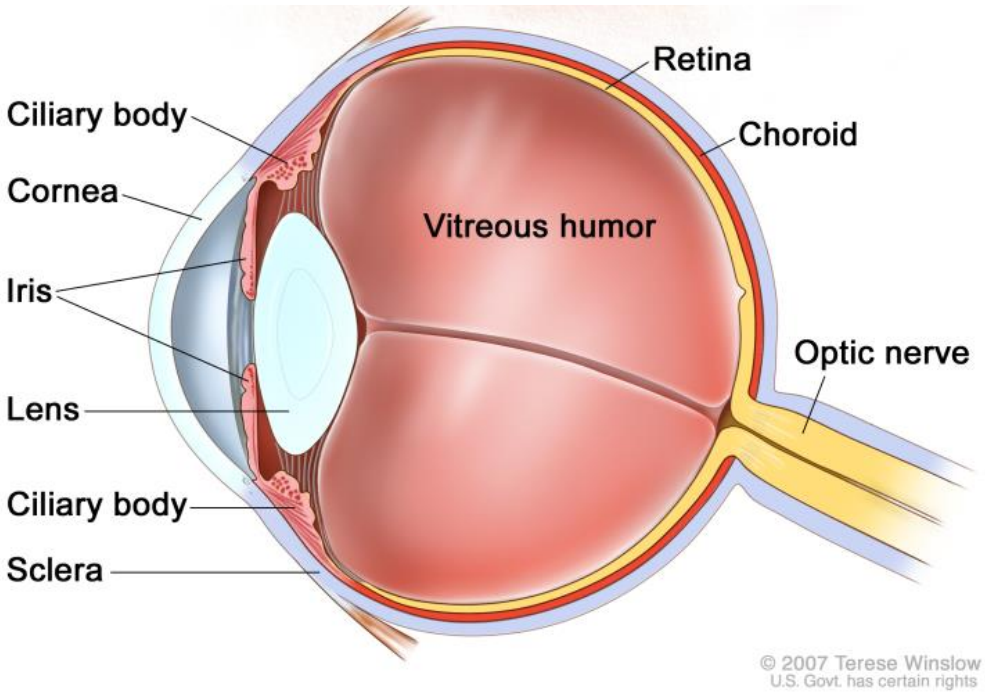

Figure 1. Anatomy of the Eye (PDQ Pediatric Treatment Editorial Board, 2002)

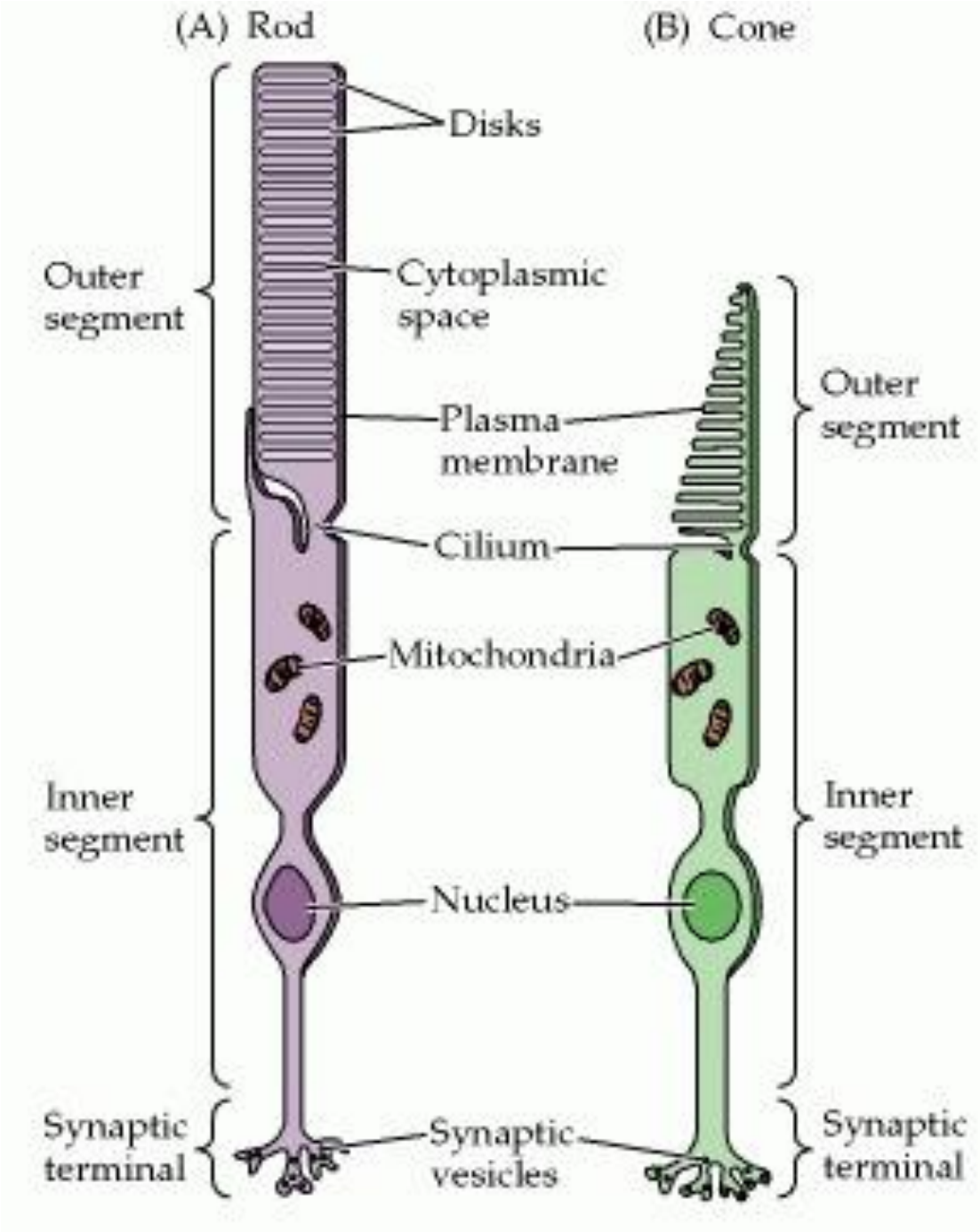

Figure 2. Structural differences between rods and cones (Purves et al., 2001)

Physiology

For humans to perceive objects, light must be transduced to electrical energy for the brain to interpret. The light must go through a series of structures that focus the light onto the retina for this to happen. The structures that concentrate the light are the cornea, aqueous humor, lens, and vitreous humor. At the retina, a complex cascade pathway involving multiple proteins and cells takes place to convert light into potential energy.

In the rods, the visual pigment that transduces light is rhodopsin. Rhodopsin is a G-protein coupled receptor (GPCR) encoded from a gene on chromosome 3. One of its components is the protein scotopsin, a seven-transmembrane helical domain. Scotopsin is covalently bound to the chromophore retinal, a vitamin A derivative. When no light is hitting the retina, the retinal is in an all 11-cis conformation, its inactive form; however, once activated from light, the 11-cis conformation is isomerized to an all 11-trans conformation to create metarhodopsin II (meta II). Meta II activates a separate protein known as G protein transducin, which releases its alpha-subunit. The alpha-subunit of the transducin will activate cyclic nucleotide phosphodiesterases that will hydrolyze cyclic guanosine monophosphates (cGMP) to GMP. Na+ channels remain open in dark conditions, allowing the rod cells to stay depolarized. However, once cGMP levels are low, cGMP-dependent channels will be inhibited, maintaining a larger volume of Na+ in the rod cells and causing hyperpolarization. This

hyperpolarization will then inhibit the release of glutamate, allowing for a cascade of different downstream neurons to either hyperpolarize or depolarize, depending on the cell type. Reverting rhodopsin to its inactive form requires rhodopsin kinase and arrestin, which restore the cGMP levels and depolarize the cell. (Ludwig et al., 2024) (Sánchez López de Nava et al., 2024)

Despite the majority of RP degeneration beginning with the rods, some mutations still start in the cones; therefore, the differences in cones should be highlighted. In the cones, the activation pathway is mainly similar to the rods, with a couple of differences. The first difference is that there are three types of cones: L-cones, M-cones, and S-cones (referencing large, medium, and short wavelength cones). S-cones are encoded from a gene on chromosome 3. In contrast, S and M-cones are encoded on chromosome X. The cone's adjacent protein, similar to rhodopsin, is known as opsin, a GPCR attached to the retinal. Lastly, the cone's response to light is less effective than that of rod cells and is quickly terminated.

The transduced signal from the photoreceptor is then transmitted to bipolar cells, which can have a range of responses depending on the subtype of bipolar cell. ON bipolar cells are activated when glutamate is low (light stimulus is present), stimulating ON ganglion cells and sending a signal down the optic nerve. OFF bipolar cells are activated when glutamate is high (no to minimal light stimulus), stimulating OFF ganglion cells. The opposite is true as high levels of glutamate will inhibit ON bipolar cells, and low levels will inhibit OFF bipolar cells. (figure 3)

RP is a cluster of mutations involving these proteins, diminishing or completely losing their function and being unable to transduce light to energy, ultimately leading to decreased vision. Though RP explicitly causes the breakdown of the RPE and photoreceptors, this physiological description explains how RP can affect the overall vision of an individual.

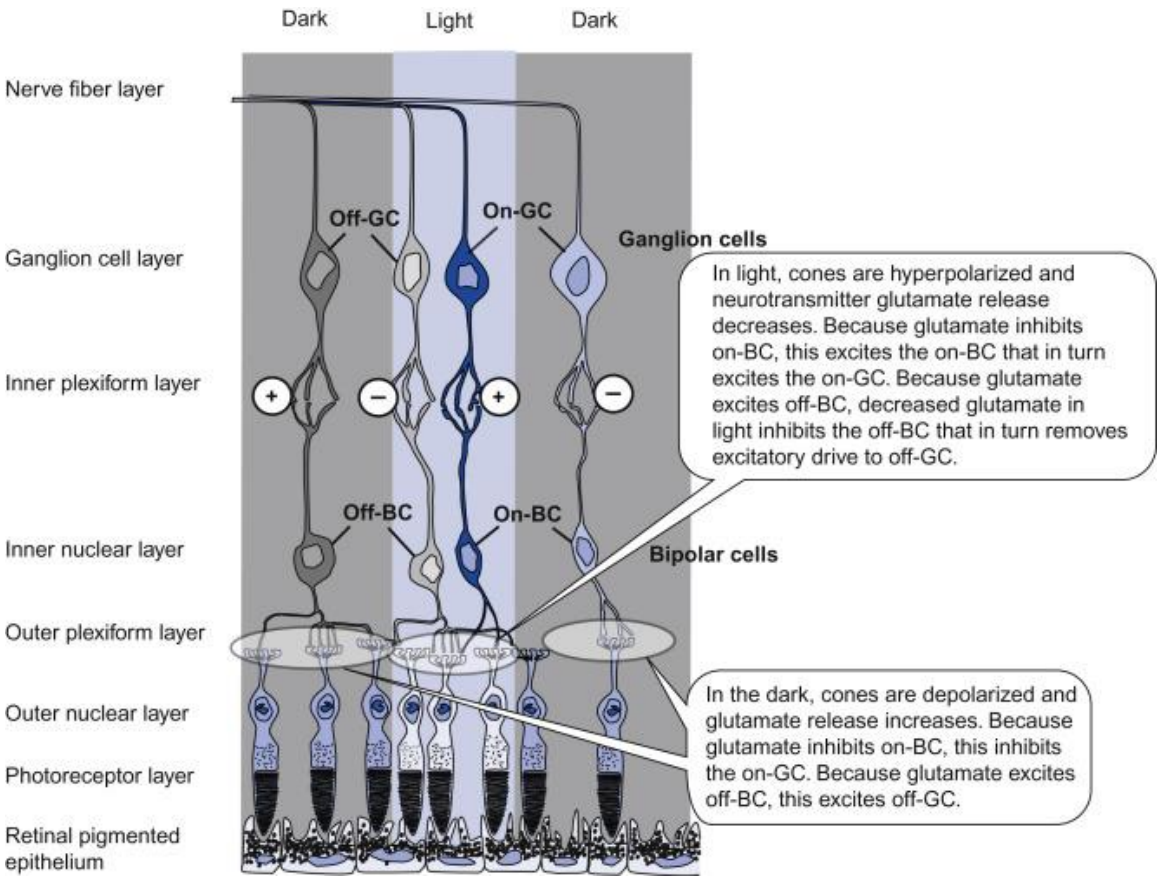

Figure 3. Physiological mechanisms of on-center and off-center ganglion and bipolar cells. (Feher, 2012)

Epidemiology and Genetics

Despite RP being the most common inherited retinal disease, it is generally known as a "rare" disease affecting approximately 1 in 3000-7000 people worldwide. (Haim, 2002) Though this number varies with increased research, recent studies show that the prevalence of RP in the United States is approximately 1 in 4000 people. (O'Neal & Luther, 2024) RP does not seem to be linked to race; however, the two main risk factors are family history and being biologically male. (Huang et al., 2022)

As mentioned, RP is an umbrella term for a group of inherited retinal mutations that exemplify similar symptoms. It is due to the heterogeneity of the disease that makes it difficult to find a treatment for RP. RP manifests in two forms: non-syndromic and syndromic. Non-syndromic RP is more common and variable, as 73 genes and over 3000 mutations have been identified. Furthermore, Non-syndromic RP can be obtained through multiple means such as autosomal dominant (20-25%), autosomal recessive (15-20%), x-linked (10-15%), sporadic/simplex traits (30%), and more. In a recent study in Italy, 591 individuals with RP (both syndromic and non-syndromic) were genetically analyzed to identify the mode of inheritance. Only 221 of the 591 participants' RP's mode of inheritance was placed, while the remaining 370 participants' RP remained unsolved. (figure 4) (Colombo et al., 2021). The study reflects how many more RP mutations have not been identified. Syndromic RP is most commonly seen

through Usher syndrome, a form of RP that also affects hearing, and Bardet-Biedl syndrome, a form of RP associated with obesity, learning disabilities, and malformations. These forms of RP have been linked to much fewer numbers of genes 15 and 18, respectively. (Daiger, 2024)

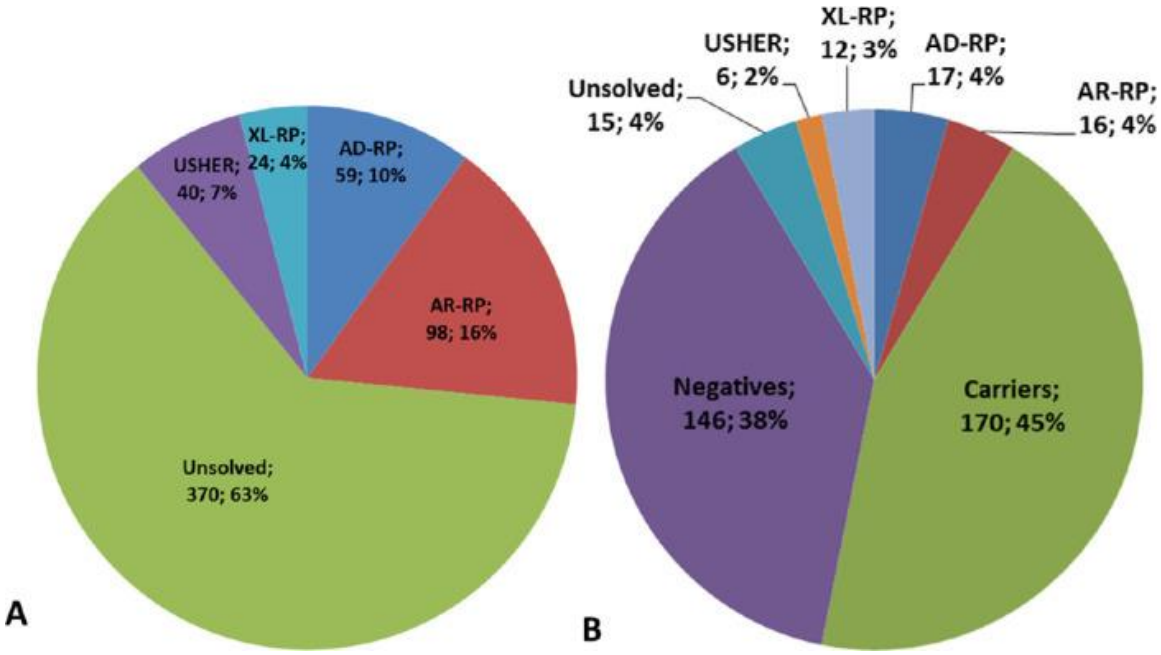

Figure 4. Prevalence of the four classes of RP based on genetic diagnosis in the whole population of 591 probands. (A) Probands, n = 591. (B) Relatives, n = 382. (Kawamura & Tachibanaki, 2008)

Diagnosis

An ophthalmologist will dilate the eye to get a clear view of the retina to diagnose RP. One of the main observable manifestations of RP is pigment deposits on the retina, called retinal bone spicules. With this observation, along with other symptoms such as loss of peripheral visual field and diminished vision at night, a physician would conduct three additional tests.

One of the exams conducted is an electroretinogram (ERG). This test will stimulate the retina with different wavelengths of light and then provide objective quantitative waveform analysis. A full ERG will have six other conditions (known as protocols) to fully capture and isolate the activity of the rods and cones. The four components of the ERG examined are the a-wave, b-wave, oscillating potential, and photopic negative response. The a- and b-waves are the two main components for an RP diagnostic examination, as the a-wave is shown as a downward deviation that will quantify the hyperpolarization of the photoreceptor cells and overall outer retinal activation. The b-wave is an upward inflection that will quantify the bipolar cells and overall phototransduction activity. (figure 5) The amplitude and implicit times, the amount of time required to reach maximum amplitude, will be examined in the analysis. In the early stages of RP, the amplitude of the waves is diminished; however, implicit time may be the same or longer. In late-stage RP, there is no detectable activity from the retina. (Jason Hsu, 2023) (Asanad & Karanjia, 2024)

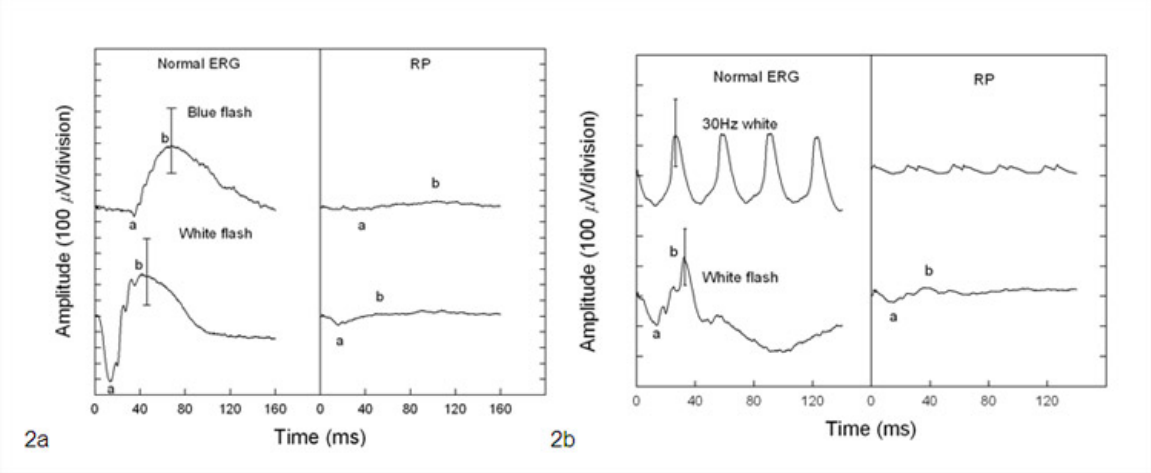

Figure 5. 2a) exemplifies normal vs RP ERG response to a flash of different colored lights 2b) exemplifies normal vs RP ERG responses to 30Hz strobe white light and a single flash of white light (Jason Hsu, 2023)

The optical coherence tomography macula (OCT) scanning technique provides a sharp, cross-sectional retina view. The OCT can be used to show abnormalities such as macular edema and retinal thinning. A physician might use this test to check for abnormalities in RP; however, it is far more often used to create a baseline for the patient and monitor the status of the retina. The OCT provides clear delineation and thickness of each layer in the retina, beginning from the inner limiting membrane to the choroid (figure 6); furthermore, an OCT angiography can further illustrate how well the retina is vascularized.

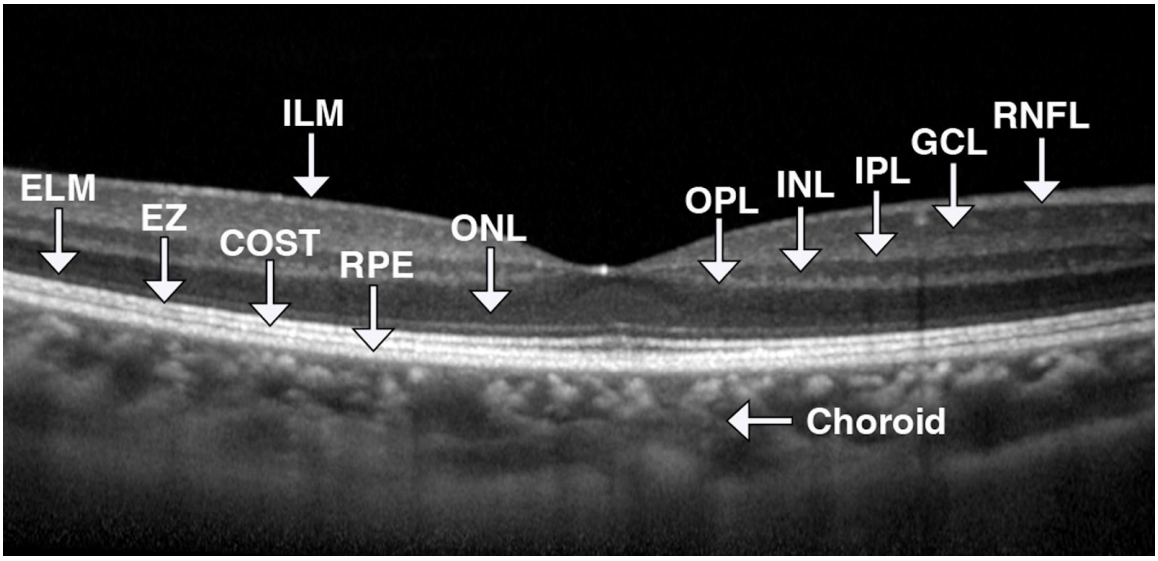

Figure 6. Optical Coherence Tomography of a Normal Control Individual. Optical coherence tomography in a healthy control illustrates the normal retinal architecture with delineation of the internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), external limiting membrane (ELM), ellipsoid zone (EZ), cone outer segment tips (COST), the retinal pigment epithelium (RPE) and the choroid. (Oh et al., 2020)

The four main components of an OCT are that a physician will monitor for loss in the ellipsoid zone (EZ), the vasculature of the retina, cystoid macular edema (CME), and overall retina thinning. The EZ in a healthy individual can be distinctly identified from the COST and RPE; however, in patients with RP, the EZ is shorter and will become indistinguishable from the COST and RPE around the edges (figure 7)

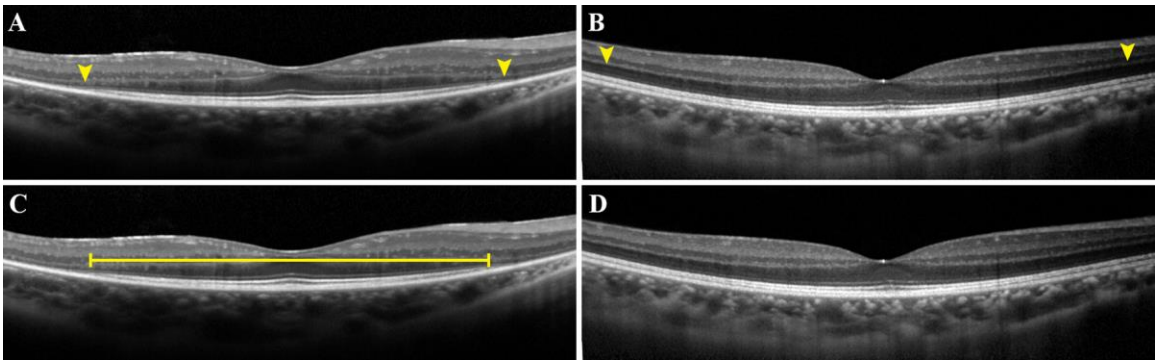

Figure 7 A)Appreciable thinning of the outer nuclear layer (yellow arrows) and loss of the delineation between the ellipsoid zone, cone outer segment tips and the retinal pigment epithelium was seen in a patient with retinitis pigmentosa. B) In contrast, the outer nuclear layer was well preserved (yellow arrows) even to the boundaries of the 30-degree field in a healthy control patient. C) The ellipsoid zone was seen to be attenuated in the parafoveal region (yellow line) in the patient with retinitis pigmentosa. D) The ellipsoid zone was seen extending past the 30-degree field in the healthy control patient. (Oh et al., 2020)

RP has been shown to diminish the vasculature of the retina, which can be detected using an OCT angiogram. (Giani et al., 2012) The OCT angiography provides four perspectives of vasculature: superficial capillary plexus (SCP), deep capillary plexus (DCP), choroid, and choriocapillaris. In the SCP, we see less detailed branching in people with RP. The DCP, choroid, and choriocapillaris have less vasculature and a larger foveal avascular zone. (figure 8)

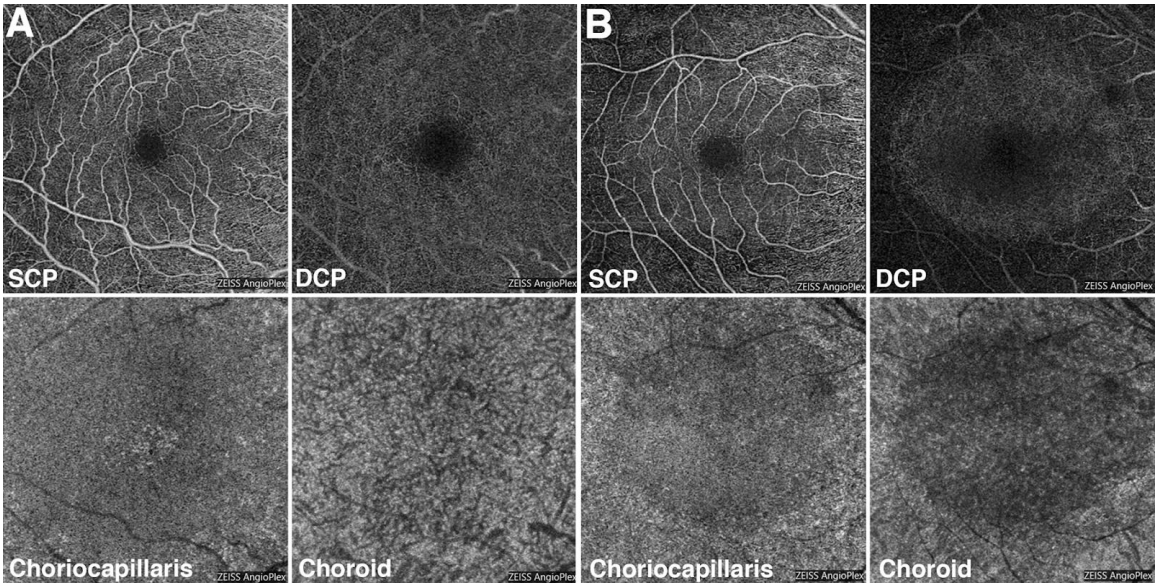

Figure 8 A)Optical coherence tomography angiography findings of a healthy, control patient demonstrated the normal retinal vasculature in the superficial capillary plexus, deep capillary plexus, choriocapillaris, and choroidal layers. B) Optical coherence tomography angiography of a patient with retinitis pigmentosa demonstrated a large demarcated foveal avascular zone in the superficial and deep capillary plexuses. The loss of vasculature was seen both in the choriocapillaris and the choroid. (Oh et al., 2020)

CME is a condition where a cyst-like swelling occurs between the retina's layers, generally between INL and ONL. (Fishman et al., 1977) This condition can occur due to multiple risk factors; however, it is also comorbid with RP. The association of retinal thickness with RP progression has been debated among researchers. (Witkin et al., 2006) It has now been distinguished that the inner retinal layer, specifically the INL, GCL, and RNFL, shows thickening due to changes in glial cell structure due to photoreceptor degeneration in RP. (Aleman et al., 2007) Diminishing thickness in the outer retina, defined as the RPE, OS, IS, ONL, and OPL, is associated with photoreceptor loss and is a better predictor of RP progression. (Witkin et al., 2006)

The visual field test maps out a person's field of vision. The exam has the patient focus on a central point while there are flashing light stimuli to which the patient must respond. (J Kevin McKinney, MD, 2022) RP diminishes vision in three different patterns. Pattern 1 is the progressive loss of the peripheral vision in a concentric pattern. (figure 9) Pattern 2 is a curved blindspot, called arcuate scotoma, originating from the nasal or temporal side of vision. Pattern 3 is vision loss in the mid-peripheral, also known as ring scotoma. (Grover et al., 1998)

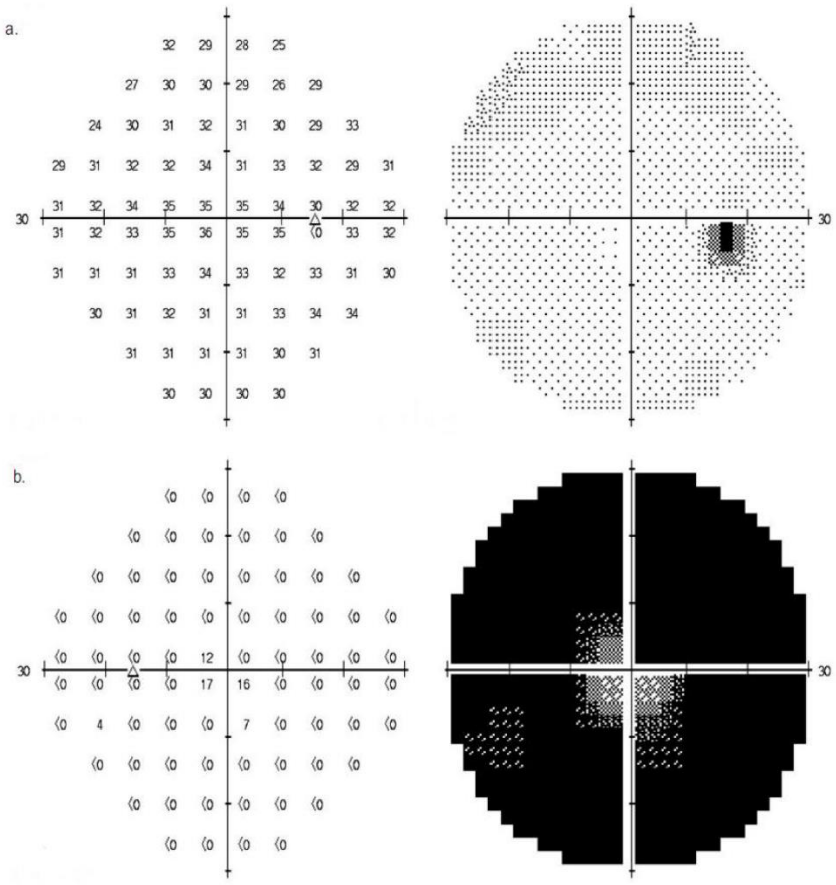

Figure 9. Visual field results (a) early stage RP (b) late stage RP (Kozma et al., 2005)

Progression

The progression of RP is broken up into early, middle, and late/end stages. The median age of onset for RP is 36.5, but it may start as early as the first decade of birth and continue after age 65. (Tsujikawa et al., 2008) In the early stages of RP, it may become increasingly difficult to see at night due to the initial degeneration of rods. There also may be diminished vision in the peripheral field in darker conditions. Despite this, there will be minimal changes to vision in daylight. (Hamel, 2006) In further examinations from physicians, there is rarely any defect in visual acuity, visual field examination, and fundus photos (figure 10a). The most important exam in identifying RP early is the ERG. The defect is generally seen as a decreased amplitude of the b-wave. (Hamel, 2006)

Figure 10a. Fundus photo of early-stage RP (Hamel, 2006)

In the middle stage of RP, it becomes increasingly apparent that there is night blindness, with tasks such as walking and driving becoming problematic in the evening. People with RP will also notice a loss of peripheral vision in daylight. This loss of vision can take on one of the three patterns mentioned above; however, a gradual loss of the concentric peripheral vision (pattern 1) is most common; this symptom of RP is verified through visual field testing. Dyschromatopsia, color blindness, is also a common symptom of middle-stage RP, usually with difficulty in distinguishing blue and yellow hues. Visual acuity also begins to diminish due to the degeneration of photoreceptors; however, RP is also an extremely comorbid disease, and loss of visual acuity can also be related to macular edema and cataracts. Fundus photo examinations will show bone spicules, narrowing of retinal blood vessels, and paling of the optic disc. (figure 10b) (Hamel, 2006)

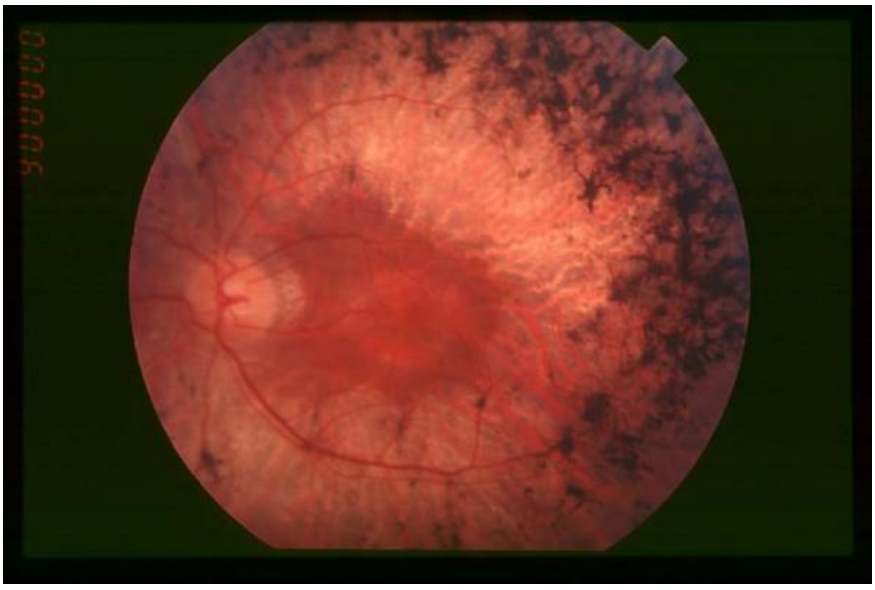

Figure 10b. Fundus photo of mid-stage RP (Hamel, 2006)

In the end stages of RP, the manifestation of symptoms remains similar to those observed in the middle stage; however, their symptoms are exacerbated. Due to the heterogeneous nature of RP, it may take 10 to 40 years to reach this stage. At this stage, there will be a complete loss of peripheral and tunnel vision, yet minor vision on fixation points may still exist. Visual acuity in at least one eye will range around 20/200, though this is not always the case as central vision may be preserved; however, magnified reading glasses are required to make out words. (Grover et al., 1999) In a fundus examination bone spicules will have reached the macula, retinal blood vessels will have become increasingly thin, and the optic disc is extremely pale. (figure 10c) ERG examinations show no response from the photoreceptors. Visual field testing shows that late-stage RP patients still have light perception in the peripheral. (Hamel, 2006)

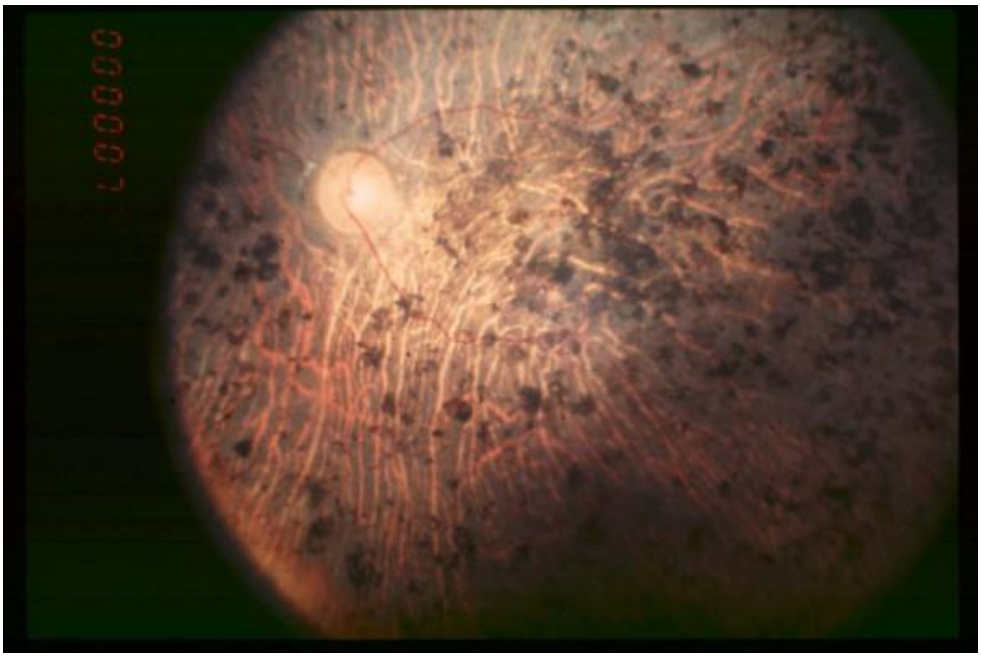

Figure 10c. Fundus photo of late-stage RP (Hamel, 2006)

Treatments

There is no current cure for RP; therefore, current treatment looks to alleviate night blindness symptoms and delay the progression of late-stage RP: (1) dietary supplements, (2) minimizing exposure to ultraviolet light, (3) cystic macular edema treatments, (4) visual aids, (5) surgery.

Vitamin A, as mentioned previously, is an integral component of the visual cycle. Studies have suggested that vitamin A palmitate supplements can delay the progression of RP, shown through a significant decrease in the decline of wave amplitudes in ERG; however, there were no significant differences in visual acuity and visual field. (Berson, 1993) On the other hand, meta-analyses have concluded that vitamin A, with and without other supplements, shows no significant delay in RP. (Rayapudi et al., 2013) The inconclusive data on vitamin A makes physicians wary of recommending the supplement to patients. This is because vitamin A is a fat-soluble molecule stored in the liver and, with high regular doses, can cause complications such as osteoporosis and liver damage. (Russell, 2000)

RP is known to be caused by genetic mutations in the RPE and photoreceptors; however, research has begun to show that neuroinflammation plays an essential part in the progression of RP. Due to the overactivation of the immune system, continuous inflammation causes the loss of neuron structure and function. (Zhao et al., 2022) Furthermore, the retina is a consistently activated structure that

requires a high metabolic rate and oxygen consumption, leaving the retina vulnerable to oxidative damage. Therefore, it is recommended to use light protection to slow the progression of RP. (Kutsyr et al., 2020)

CME is a common complication that arises in RP patients. It is estimated that 10-50% of RP patients also suffer from CME. (Strong et al., 2017) CME is the swelling of the retina due to fluid buildup in between its layers, which can cause blurring of central vision and possibly contribute to the degeneration of the retina. There are many successful treatments for CME, such as intravitreal steroid injections, oral corticosteroids, and anti-VEGF injections. (Bakthavatchalam et al., 2018) Though this method may not delay the progression or presence of RP, it can reduce further complications and alleviate some of the symptoms of the disease.

Visual aids that amplify light have also been developed to assist RP patients with night blindness and improve their quality of life. Two primarily used low-vision mobility devices are night vision pocket scope and goggles. Research with night vision pocket scopes has shown that RP patients have the same visual acuity in dimly lit conditions with the assistance of a pocket scope as their vision in daylight. (Berson, 1973) Night vision goggles have been shown to minimize the amount of bumping into different objects in all settings; furthermore, the study has shown to increase the percentage of preferred walking speed in specific settings such as residential areas. After the study, patients showed an increased

sense of mobility, independence, orientation, and tranquility. (Hartong et al., 2004) Finally, research has shown that certain visual aids perform better for patients, and research into the ergonomics and functionality of these devices can be improved. (Mancil et al., 2005)

Surgical intervention with the ARGUS II prosthesis is an option for patients with end-stage RP and minimal light perception. ARGUS II prosthesis has three main components: a camera attached to the patient's eyewear, a video processing unit (VPU) worn around the waist, and an epiretinal microelectrode-array implant that is connected to the antenna on the actual prosthesis and sutured to the sclera. (Rohan Bajaj et al., 2019) (figure 11) The camera recorder will capture images and send these signals to the VPU. The VPU will then process and convert the electrical signals to a brightness map. This image will then be transmitted from the primary to the secondary antenna; from here, the signal is submitted to the electrode array, which will stimulate the retina. This intervention will allow RP patients to see lines and shapes and has been shown to increase patients' scores on visual tests. However, over one-third of patients reported issues with the surgery or prosthesis, such as conjunctival erosion, conjunctival dehiscence, hypotony, and endophthalmitis during the phase II clinical trials. (Bulcha et al., 2021) Recent updates about the intervention have shown that more research is being done to minimize the number of complications and improve the quality of the device. (Rohan Bajaj et al., 2019)

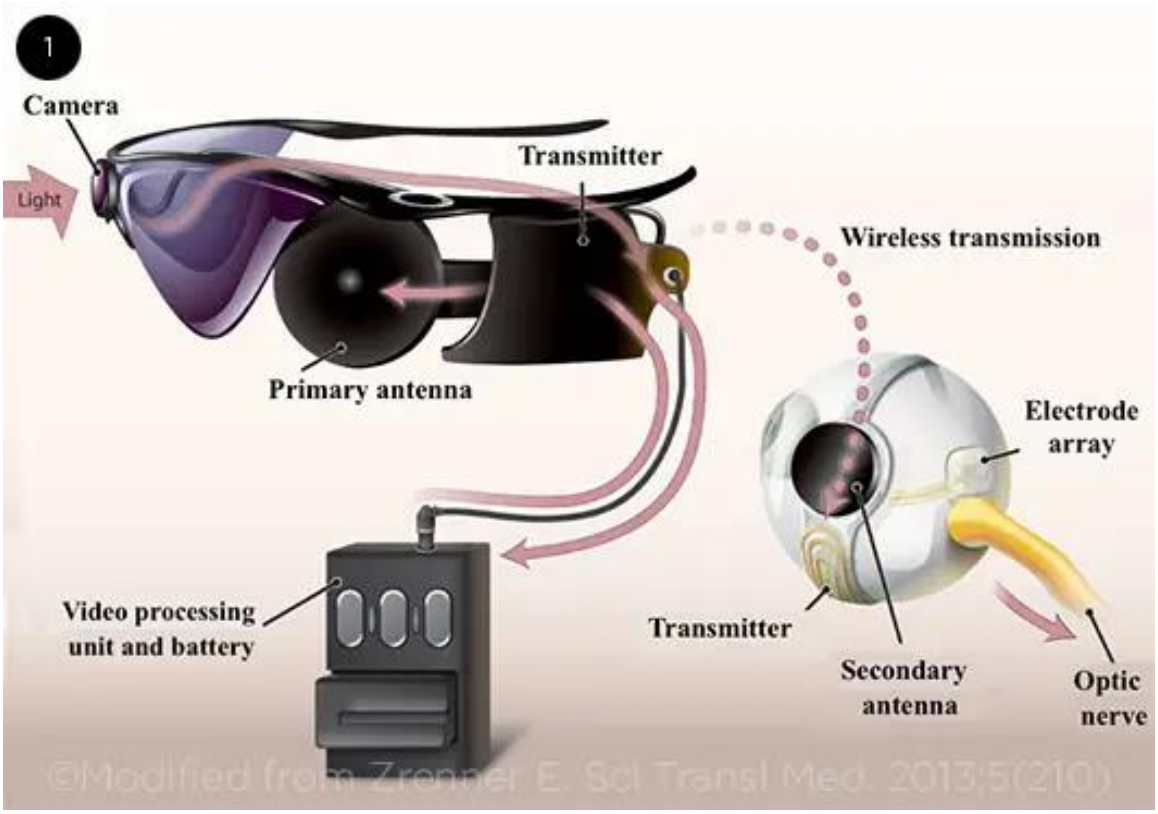

Figure 11. Components of the ARGUS II system (Rohan Bajaj et al., 2019)

Future Therapy

Gene therapy is the treatment of disorders through the complementation of an engineered piece of new DNA, modification, or removal of existing DNA. This field of research has become increasingly popular for genetic diseases, such as RP, due to the treatment's potential to cure the disorder at the root of the cause. Due to the heterogeneous nature of RP, mutations can either cause the loss of function in a protein known as recessive RP, or in dominant RP, there is a gain of function that is detrimental and requires gene suppression. (K. Y. Wu et al., 2023) The three primary forms of gene therapy currently being researched for a solution for RP are viral vectors, CRISPR, and RNA replacement.

Viral vectors are commonly used to integrate genetically modified DNA into a cell.The three primary forms of vectors of interest are adenoviruses (Ad), adeno-associated viruses (AAV), and lentiviruses (LV). (Bulcha et al., 2021) AAVs have become the most widespread virus of interest due to their size, allowing the accurate targeting of the retinal layer. AAV also shows further promise as they are unlikely to initiate an immune response, will enable the target gene to be expressed for long periods, have the possibility of a second dose in the subretinal space, are unable to auto-replicate and express in humans, and are non-pathogenic to humans. (Bulcha et al., 2021) (Trapani et al., 2014) Viral vectors are used for recessive RP and to bring back the function of proteins that have been mutated. One of the drawbacks of using AAV vectors is that they

cannot work with large genomes, require second-strand synthesis, and the highly invasive nature of subretinal injections to integrate the AAV. (Trapani et al., 2014)

CRISPR is a gene editing method that can edit genes to allow for gene expression and suppression. (Xu & Li, 2020) The CRISPR-cas9 gene editing technique uses non-homologous end joining to silence dominant RP mutations. This method has proven to be consistently successful in vitro experimentation; however, it has many more complications in therapy applications. The complications arise due to the particular requirements of the guide RNA, characters of the cell type, and individualized factors of the host. (K. Y. Wu et al., 2023)

CRISPR-cas13 is a newer editing method using an RNA-based endonuclease to modify genes during transcription. (Hu et al., 2022) (Botto et al., 2021) CRISPR-cas13 has been proven to restore the function of proteins in monogenic diseases. Though this method is unfit for RP because it is a heterogeneous disease often affecting multiple genes, this research shows that we can edit genes and bring back functionality to specific cells. The two main complications with the cas 13 endonuclease are the nonspecific cleavage of the protein and the possible toxic effects on neural cells. (Q. Wang et al., 2019; Q.-W. Wu & Kapfhammer, 2021) The potential toxicity of cas 13 is especially alarming as the RPE and retina are a network of neurons.

RNA replacement is a gene therapy that represses coding RNA translation into protein. In RP, the goal is to have a regulatory noncoding RNA target and bind to mutated messenger RNA (mRNA) sequences; this process would repress the amount of dysfunctional protein synthesis and, therefore, would be used to treat recessive RP. There are three types of noncoding RNA used as regulatory elements: micro-RNA (miRNA), small interfering RNA (siRNA), and short hairpin RNA (shRNA). miRNA hinders post-transcriptional modification by specifically binding to the binding site of the mRNA, causing translational repression; in addition, mRNA becomes destabilized and quickly deteriorates. (Gemayel et al., 2021) siRNA is a double-stranded RNA that acts similarly to miRNA; however, the practical clinical difference is that siRNA is highly specific and can distinguish the difference in a single nucleotide. Finally, shRNA has a similar structure to miRNA; its mechanism of action is different as it affects DNA delivery and activates an RNA-induced silencing complex (RISC) that either represses or helps degrade the mRNA. (Gemayel et al., 2021) One of the main concerns is that siRNA is easily degraded; therefore, there is more focus on ShRNA's use as it is more consistent and potent.

Stem cell therapy vision in RP patients through two methods. The first method replaces the degrading RPE and photoreceptors with stem cells, and the second restores the degenerating RPE and photoreceptors by releasing trophic factors. The main goal of cell therapy is to have long-term integration and form stable synaptic connections between these newly functional cells and the host.

[60] This treatment will look at four different types of stem cells ((1) embryonic, (2) bone marrow-derived stem cells, and (3) stem cells derived from RPE) that can be used to restore vision and their potential limitations.

Embryonic stem cells can give rise to any of the three types of germ layers. A consequence of using embryonic stem cells is the potential immune response due to the cells having to come from a human embryo. Induction of pluripotent stem cells, generally derived from skin or blood reprogrammed to an embryonic-like state, is preferred. (Ye et al., 2013) Because these cells are not derived from an embryo but from the host, there is a minimal chance of an immune response. Replacing damaged RPE and photoreceptor cells with induced pluripotent cells may delay the progression of RP and restore vision. (Kashani et al., 2020) In a study conducted in 2021, researchers injected human induced pluripotent stem cells (hiPSC) derived retinal cells into mice. The experiment showed more significant functions of photoreceptors and RPE, measured through the expression of cones, rods, and neural retina proteins. (Ye et al., 2013) In addition, other studies throughout the year have shown that with the intervention of stem cells, there were increases in tight junction protein, pigmentation, ciliation, and higher levels of growth factors in the retina. When hiPSC was injected into the atrophic retina of pigs, there was a delay in disease progression. However, epigenetic memory has limitations, wherein the cells maintain gene expression patterns from the parent cell, which could influence the properties of

hiPSC when injected. Furthermore, the induced pluripotent cells can proliferate indefinitely, increasing the risk of teratoma formation. (K. Y. Wu et al., 2023)

Bone marrow stem cells are the primary type of cell researched as a potential therapeutic for RP. (Ferroni et al., 2013) Bone marrow stem cells are embryonic tissue-specific cells (figure 12) and can give rise to a select group of cells. Bone marrow stem cells come in two forms: hematopoietic and mesenchymal stem cells. Hematopoietic stem cells are tissue-specific stem cells that can differentiate into blood cells, such as white blood cells, red blood cells, and platelets. Mesenchymal stem cells can differentiate into skeletal tissues, such as cartilage, bone, and fat. (Pittenger et al., 2019) Research is unsure if bone marrow stem cells can differentiate into RPE and photoreceptors. Instead, research primarily focuses on the antiangiogenic and neurotrophic factors researched from these stem cells. These cells have been demonstrated to release insulin-like growth factor-1 (IGF-1), class II major histocompatibility complex (MHC class II) antigens, and Th2-related cytokines, which have been shown to provide anti-inflammatory responses. Researchers have been able to integrate mesenchymal-derived progenitor cells into mice and been able to track an anti-inflammatory response. (Brown et al., 2022)

Stem cell-derived RPE releases neurotrophic factors that can provide support for photoreceptors. Research in mice with retinal degradation has shown that stem

cells can release ciliary neurotrophic factors that protect photoreceptors from degradation. (Talcott et al., 2011)

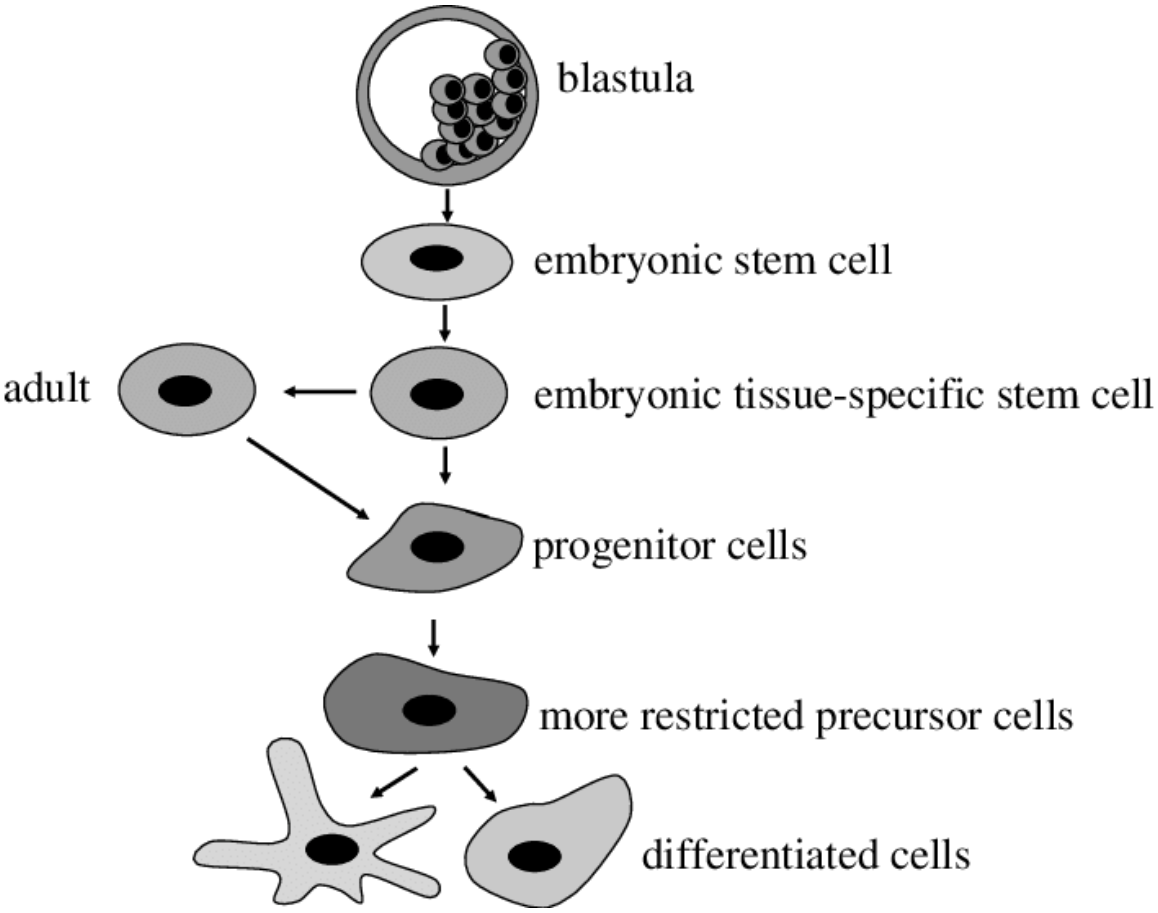

Figure 12. A model of how pluripotent embryonic stem cells undergo maturation and progressive restriction in their developmental potential. Initially, tissue-specific stem cells, e.g. neural, hemopoietic, hepatic, etc., are generated. These stem cells proliferate and may mature during development but retain their differentiation ability. Tissue-specific stem cells do not generate fully differentiated cells directly but do so by first generating intermediate precursors or blast cells that undergo limited proliferation and ultimately mature to generate fully differentiated progeny.(Magnus et al., 2008)

While great strides have been made in developing gene and stem cell therapeutics in RP, it cannot compensate for the losses of function. Gene therapy

has been shown to have limitations in treating patients with undiagnosed RP mutations and advanced stages of RP. Furthermore, this therapy is focused on individualized care, which can become costly and inefficient. As a potential cure for RP, optogenetics takes on a one-for-all approach. Optogenetics is a technique that introduces optical proteins into the DNA of target cells to control and monitor specific neurons. (Duebel et al., 2015) In RP, optogenetics aims to convert non-light-sensitive retinal cells, for example, bipolar cells and retinal ganglion cells, into artificial photoreceptors by incorporating opsin, a light-sensitive protein, into the cells. The treatment has more nuance as the method and target cell will distinguish between depolarizing (on-cell) or hyperpolarizing (off-cell) opsin. (Tomita et al., 2009)

Microbial opsin (Type 1) is an all-trans chromophore and, upon activating the visual cycle, has a conformation shift that affects ion channels. (F. Zhang et al., 2011) Garita-Hernandez and colleagues observed the membrane trafficking and toxicity potential of microbial opsin in human-derived organoids. (Athanasiou et al., 2018) They theorized that microbial opsin injections into retinal organoids predict in vivo applications. Recent studies have shown that certain strains of microbial opsins can restore cells and improve vision. (Garita-Hernandez et al., 2018)

Animal-derived opsin (Type 2) is in an 11 cis retinal confirmation and indirectly affects the ion channels through a GPCR cascade. (F. Zhang et al., 2011) This

method targets ganglion cells and is administered intraventricular injection of mammalian ionotropic glutamate receptors. This study has been shown to restore vision in visible light and shows evidence of increased light responses. The study was further done in larger animals with longer life expectancies, showing partial gain of vision, increased efficiency in maze tests, and increased ERG response. (Nikonov et al., 2022)

Neuroprotective agents are peptides that can be used with other therapeutics to slow the progression of RP. Some agents used to protect the retina are antioxidants, anti-apoptotic agents, neurotrophic factors, ciliary neurotrophic factors (CNTF), brain-derived neurotrophic factors, and fibroblast growth factors. (K. Y. Wu et al., 2023) A limitation of these agents is that they are quickly degraded; however, Yang et al. showed that when CNTF and Oncostatin M, an immunosuppressant, were incorporated into a nanoparticle, the retinal ganglion progenitor cells survived longer. (Yang et al., 2021) In conclusion, the use of neuroprotective agents holds promise in attenuating the progression of RP in the early stages of the disease. In tandem with optogenetics, stem cell therapy, and gene therapy, neuroprotective agents can be used as supportive therapy that could yield better results for RP patients.

Sahaboglu et al. observed that damaged RPE cells released exosomes that were directed toward non-damaged cells and promoted new blood vessel growth. (Sahaboglu et al., 2019) Through this observation of exosomes, research has

begun to look at the possible therapeutic effects in patients with RP. Exosomes are extracellular vesicles that have budded off of a cell and could contain nucleic acids, proteins, lipids, and metabolites. (Kalluri & LeBleu, 2020) Three types of exosomes derived from different models have been researched and shown promising therapeutic effects, which will be discussed below.

Mesenchymal-derived exosomes have been shown to have therapeutic properties for RP. Induced retinal detachment in Sprague–Dawley rats has produced mesenchymal exosomes that diminish Tumor Necrosis Factor-alpha and IL-β (inflammatory cytokines) and decrease apoptosis in photoreceptor cells. (Ma et al., 2020) Furthermore, mesenchymal exosomes have been shown to inhibit immune cells such as microglial cells and macrophages. (J. Zhang et al., 2022) RPE-derived exosomes have shown results that could treat RP. In mice that have induced retinal detachment, exosomes have been shown to restore damaged photoreceptors, diminish inflammation, and inhibit the apoptosis pathway. (Y. Wang et al., 2021) Neural progenitor cells derived from exosomes have also been shown to possess anti-inflammatory and anti-apoptosis properties. (Bian et al., 2020)

Psychosocial impacts

Numerous studies have shown the psychological impacts RP can have on a person's life. The ramifications of having a chronic, incurable diagnosis, in addition to the unpredictable progression of RP, have been shown to increase

the intensity of emotions such as sadness and fear. Though these emotions generally come with learning about the diagnosis, there are further burdens that appear with the progressive stages of RP. In the early stages of RP, there will be no impact on the ability to perform daily activities (ADL); however, early symptoms of night blindness can lead to unease and fear. (Farmer et al., 2020) In the middle stages of RP, night blindness and low visual acuity will significantly reduce their ADL. Moreover, low visual acuity correlates to lower quality of life and psychological comorbidities. (Jangra et al., 2007) A questionnaire with the majority of the participants having mid-stage RP showed that there was a higher prevalence of hypochondria, hysteria, paranoia, antisocial behaviors, obsessive-compulsive disorder, depression, schizophrenia, and hypomania than the general public. (table 1) (Adhami-Moghadam & Iran-Pour, 2014) In late-stage RP, there is a loss of autonomy and independence. The next part of this section will delve into four prevalent burdens experienced by individuals in the mid-to-late stages of RP population experience: physical, financial, quality of life/psychological, and societal, in addition to their implications.

RP can significantly impact a person's mobility and ability to carry out tasks such as eating, driving, reading, and shopping. Examples of the physical manifestation of these burdens are difficulty walking at night, inability to recognize and greet people, and higher risks of injury due to reduced mobility. (Chaumet-Riffaud et al., 2017) RP can also shorten and lower the quality of sleep as rod degeneration

leads to less light input to the brain, putting RP patients at higher risk for cardiovascular and metabolic disorders. (Gordo et al., 2001)

As patients begin to lose their ADLs, their independence diminishes, necessitating the involvement of a caregiver. With early/pediatric onset, this responsibility falls on parents. The physical and emotional responsibilities of a caregiver will often lead to a parent's psychological burden. The challenges and stress of the role of a caregiver can evoke feelings of anger and result in parents lashing out, which can strain the relationship. (Palamaro Munsell et al., 2012) In addition, with the progression of night blindness, RP patients have difficulty attending social settings and activities such as movie theater, concerts, and dining out at night. These struggles may lead to withdrawal from society and feelings of loss of identity and social isolation. (Chivers et al., 2021)

Lastly, the decrease in quality of life with the progression of RP often leads to psychological burdens. RP patients have been found to have higher levels of psychological distress compared to controls with and without complications due to the early onset and incurable nature of the disease. (Garip & Kamal, 2019) In a survey conducted in the UK, 92% of RP patients reported that the disease takes a toll on their mental health. (Farmer et al., 2020) Patients are also aware of visual impairment stigmas in social and workplace settings, often subjecting them to denigration, avoidance, and moral disapproval. (Allen & Birse, 1991) If patients cannot formulate proper coping mechanisms, such as canes, these

consequences can be exacerbated when more visible visual aid is required. (Garip & Kamal, 2019) Furthermore, the progressive nature of the disease requires RP patients to continuously adapt and resign themselves to the gradual decline in vision, which can lead to feelings of anxiety. (Farmer et al., 2020) As the quality of life diminishes and they lose the ADL, patients report increased thoughts of suicidal ideation, loss of enjoyment in life, irritability, and sadness. (Mojon-Azzi et al., 2008) Finally, the accumulation of physical, financial, quality of life/psychological, and societal burdens of RP can further take a psychological toll.

Impact of RP in work and goals

RP can also amount to a financial burden as it can impede one's career promotions and ability to attend school. This burden is particularly unique to RP due to its tendency for early onset and potential impact during critical stages of learning and development. Clinical experts emphasize that students with RP will need considerable support in schools to ensure their optimal preparation for academic success. (Farmer et al., 2020) At the age of 40, approximately 61.5% of RP patients are employed, which is significantly lower than the general population (about 83.9%). The progression of the disease also correlates with a decreased employment rate, as one study showed 79.5% employment in low-vision RP patients compared to 67.6% employment in blind RP patients. (Chaumet-Riffaud et al., 2017) Employment has also been shown to give people

a sense of purpose and a critical component of mental health. With RP patients increased difficulty in obtaining and maintaining employment, this may also lead to an increased prevalence of mental disorders. (Drake & Wallach, 2020) Furthermore, due to the stigma of disability status, approximately half of RP patients are apprehensive about obtaining disability benefits due to fear of discrimination in the workplace. (Chaumet-Riffaud et al., 2017) Lastly, there is an increased financial burden in disease management, ranging in the cost of transportation, hospital visits, and extra home assistance.

Meta-themes for improvement in quality of life

Garip and colleagues filtered through 5124 studies and found 12 papers that possessed four different requirements: qualitative studies with adults living with RP, studies focusing on patients experiences of living or coping with RP, RP impact on quality of life of patients, and studies with 75% or more of participants being diagnosed with RP. The study evaluated first order, patients' first-hand experience with RP, and second order, the researcher's interpretation of patients with RP experiences, to formulate four overarching meta-themes linked to the quality of life in RP patients: (1) experience with the healthcare field and social support, (2) managing one's identity with RP, (3) living with the practical and emotional issues with RP, (4) and adaptive/maladaptive coping mechanisms. This portion of the study will discuss these themes in depth and then formulate

an intervention to address these concerns adequately and improve the quality of life.

Managing one's identity with RP

This theme explores when patients with RP first notice symptoms when they are diagnosed, the adjustment to the diagnosis, and addressing concerns of independence. When patients with RP are first diagnosed, many patients report feelings of despair, fear, and devastation. Furthermore, reports of decreased confidence resulting from the progressive loss of vision symbolize a diminished sense of independence and autonomy. (Bittner et al., 2010) (Fourie, 2007) (Thurston, 2010)

Many patients at this stage begin to look for reasons why they have RP and the meaning of their diagnosis; this journey for an answer could either be scientific or spiritual means making. (Hayeems et al., 2005) With the initial diagnosis of RP, patients realize that previous activities and habits may no longer become possible. The APA defines identity as " a sense of continuity, or the feeling that one is the same person today that one was yesterday or last year." During this stage of the conflict, patients report a sense of deprivation as they lose a sense of pleasure, vision, social support, and interest in hobbies. (Fourie, 2007) With the cognitive dissonance in one's current identity and possible encroaching disabilities of RP, patients must begin to adjust their identity with RP or maintain their self-identity as being sighted and conceal visual impairments. (Fourie, 2007)

Living with practical and emotional issues of RP

As RP progresses, day-to-day tasks such as dressing oneself, cooking meals, commuting to school or work, and grocery shopping become increasingly difficult. The growing challenge of routine tasks due to the progression of RP may further impact lifestyle choices; for example, difficulty in grocery shopping and cooking meals may lead to eating frozen or fast food, affecting their nutritional health. Furthermore, individuals may have an increased fear of burdening their support system and having to depend on them in situations such as needing help with transportation for social gatherings might make them choose to skip events altogether. This decision can deepen feelings of isolation, reducing crucial social interactions meaningful for emotional balance amidst RP's progression. Emotional states felt in the initial stages of RP, such as fear, isolation, and vulnerability, may be exacerbated as RP patients begin to experience difficulties in performing practical tasks. This section illustrates the struggles of coping with practical and emotional challenges linked to RP. It also demonstrates how these struggles may inadvertently lead to making detrimental lifestyle choices, further compromising their health.

Experience with the healthcare field and social support

In experiences with receiving their diagnosis of RP, patients recount their interactions with physicians as blunt, vague, or mild. The most common theme was bluntness, which left many patients feeling devastated. One patient reports,

"He said, 'By the time you're 50, you're not going to be able to drive…I was completely devastated. I was 30 years old… the end of my life felt like it occurred that day." Patients reporting vagueness in receiving their diagnosis felt anxious about not fully understanding the disease. A patient explains, " He told me I had RP but didn't tell me I would likely go blind…I went through a lot of anxiety attacks because I had no knowledge of what was actually going to happen." [87] Patients who recounted a mild tone in their dialogue with physicians experienced hope. A patient explained, "He said, 'It's a progressive disease. It's a long slow process… it could happen in five years or in 50 years'…so I chose to hope it would happen in 50 and move on. Patients turned to healthcare workers for intellectual, practical, and emotional information to understand RP but were met with unfilling interactions. (Hayeems et al., 2005) Counseling is a subsequent step recommended to patients, which has been shown to help alleviate many of the symptoms previously mentioned; however, many RP patients do not choose to receive counseling. In a study of 143 visually impaired individuals, 27.35 reported symptoms of mild to severe depression, yet only 12% were prescribed antidepressants, and none were receiving counseling. (Rees et al., 2010) This section highlights the unfilled needs of many RP patients in their interaction with physicians and the multitude of patients experiencing mental health problems without any counseling.

Adaptive and maladaptive coping strategies

The paper has consistently highlighted how RP disproportionately impacts this population's mental health; however, there is a portion of patients who overcome the difficulties of managing RP. The meta-analysis has found that the resilience of these patients comes from the use of adaptive vs maladaptive coping mechanisms. (Garip & Kamal, 2019)

Adaptive coping mechanisms, such as problem-focused coping strategies, address the problem by taking action to make the situation achievable. (Algorani & Gupta, 2024) Problem strategies for RP patients can include scheduling appointments and errands during the day when they have the best vision, allocating more time for transport to unfamiliar places, and using visual aid instruments. (Falchetti et al., 2016) Social coping strategies reduce stress by seeking social support. (Algorani & Gupta, 2024) Understanding RP with family and friends can help outline the emotional and physical support the individual expects. Social coping also allows individuals to adjust to this new identity, making dealing with social situations and progressive vision loss more manageable. (Falchetti et al., 2016) Emotion-focused coping used downward social comparison to feel grateful for their situation and the abilities they still had remaining; even in times of fatigue, the severe tiredness was overshadowed by a feeling of gratitude when patients utilized emotion-focused coping. (Schakel et al., 2017) Others engaged in maladaptive coping strategies, which meant

individuals avoided accepting their condition and addressing their problems; instead, they would engage in unhealthy coping mechanisms such as smoking and more sedentary lives. (Rees et al., 2010) We see here how the coping mechanisms one utilizes in challenging situations can influence the other meta-themes and overall quality of life in individuals with RP.

Proposed Design Therapy Model

This proposed model will address the four meta-themes to increase the quality of life of individuals with RP. The model will begin with patients' interactions with physicians during diagnosis and enrollment into therapy. In the counseling portion, the paper will delve into managing identity and developing robust coping mechanisms, which, if worked on, could improve practical and emotional issues with RP.

The objective of this section is to address the concerns of the patient and physician, specifically the ophthalmologist, regarding interaction when given the diagnosis of RP. There is a significantly lower number of articles about breaking bad news in ophthalmology compared to other specialties; furthermore, as of 2016, there was no known formal training in ophthalmology to break bad news to patients. (Hilkert et al., 2016) In a Medscape survey of physicians, 41% of ophthalmologists reported spending 9-12 minutes with patients, which was the shortest time of all specialties. (Sarah Grisham, 2017) As previously mentioned,

the majority of RP patients report feeling devastated after receiving their diagnosis in a blunt tone. (Hayeems et al., 2005) Many protocols for breaking bad news have been developed throughout the years, and the one used explicitly by oncology is the SPIKES protocol. The SPIKES protocol is an acronym that stands for setting, perception, invitation, knowledge, emotion, and summarization. The protocol allows physicians to gather information and understand the patient's perspective, inform the patient of the diagnosis, provide support and empathy during the conversations with the patient, and create a patient-centered collaboration in treating the diagnosis. (Baile et al., 2000) In a study piloting the integration of the SPIKES protocol in ophthalmology, 76% of residents agreed on a structured lesson in breaking bad news, and 100% reported that they would use this protocol in the future. (Hilkert et al., 2016) Proper use of the SPIKES protocol would reduce devastation when receiving their diagnosis, allow patients to feel included in managing their health, and receive intellectual information about their diagnosis.

The first objective of counseling is to help individuals integrate RP and its visual impairments into their identity. Identity inconsistencies in attempting to identify as visioned while visual impairment progresses can lead to depression and social isolation; however, when RP is integrated into one's identity, RP patients have an easier time adjusting to progressive impairments. Thurston proposes the utilization of pluralistic counseling for the visually impaired. Pluralism is the belief that no single perspective is universally true and, therefore, impossible to reduce

the subject of matter's interconnectedness, complexity, and uniqueness. (Smith et al., 2021) Using pluralism, Thurston created a therapeutic task list encapsulating the topics patients may want to explore. This list could be modified into three categories (past, present, and future) that will allow the patient to explore how RP has and will impact their life. The objective of this modification is to still integrate pluralism by allowing patients to emphasize particular areas or struggles with RP, in addition to RP understanding of the impacts RP may have had and allowing for exploration of their future in hopes of incorporating RP into their identity.

The second objective of counseling is to develop robust coping mechanisms for individuals with RP. Coping theory is the cognitive and behavioral adjustments to external and internal difficulties. (Lazarus & Folkman, 1984) Maladaptive coping mechanisms have been shown to have detrimental effects on physical, psychological, and social ripple effects, while adaptive coping mechanisms allow individuals to manage and overcome challenges.Furthermore, coping skills are generally automated unless conscientiously worked on. To have patients adjust this autonomic mindset to use adaptive coping, I suggest employing cognitive behavioral therapy (CBT). Montazeri and colleagues evaluated the use of CBT in Iranian women with multiple sclerosis, a chronic autoimmune disease. At the end of the study, patients enrolled in CBT courses were more likely to use problem-oriented coping skills and less likely to use avoidance-oriented coping skills than the control group. (Montazeri et al., 2022) Edraki and colleagues evaluated

coping skills training concerning depression, anxiety, stress, and self-efficacy in type-1 diabetic adolescents. The study conducted an eight-week coping skills training program that went into a different topic each week: ((1)Introduction, (2)Recognizing the disease, (3)Principles of self-care, (4)Stress management, (5)Communication skills training, (6)Cognitive-behavioral modifications, (7) Problem-solving, and (8) Final) The experiment showed a significant reduction in depression, anxiety, and stress for adolescents who were apart of the intervention compared to the control group. (Edraki et al., 2018) I propose a similar style of coping skills training for RP patients; however, I further employ a pluralistic perspective that would allow patients to integrate RP into their own identity. In addition, emphasize the topic of cognitive behavioral modification to modify and enhance adaptive coping skills.

DISCUSSION/CONCLUSION

In conclusion, the literature review focuses on patients' lives with RP, revealing several themes that impact their quality of life. These themes include patients' challenges in managing their identity, coping with practical and emotional issues, navigating interactions with healthcare professionals, and using adaptive or maladaptive coping skills.

One crucial aspect is the initial diagnosis experience for patients, commonly characterized by feelings of devastation and anxiety. Patients then struggle to get the emotional, intellectual, and practical information to reconcile their sense of self with the diagnosis. Practical tasks become increasingly complex with the progression of RP, which impacts daily routine tasks, leading to potential poor lifestyle choices and emotional distress. Furthermore, the lack of a protocol for breaking bad news for patients in the field of ophthalmology can lead to interactions with healthcare providers, who often need more empathy. The paper has identified that amidst these challenges, there is hope in helping patients find their new sense of identity and integrate adaptive coping mechanisms. Problem-focused approaches, social support seeking, and emotion-focused approaches can reduce the negative impact of RP.

To address these complexities and deficits in RP patient care, a comprehensive therapeutic model is proposed to improve the quality of life for RP patients. This model addresses varying patient-physician interactions by adopting a protocol for

breaking bad news similar to the SPIKES protocol used in oncology. The protocol will emphasize empathetic and informative communication during diagnosis and help facilitate patient-centered care. Furthermore, counseling will aim to address the integration of RP into their identity and coping skill issues by using pluralistic counseling and cognitive behavioral therapy.

While there is consensus on the need for interventions to enhance RP patients' quality of life, controversies may arise regarding the implementation and efficacy of specific therapeutic approaches. Limitations such as access to specialized care and individual variability in response to interventions must also be considered.

In essence, addressing RP patients' multifaceted challenges requires a holistic approach encompassing practical support and psychological interventions. By fostering resilience and empowering individuals to adapt effectively, it is possible to enhance their quality of life and promote well-being despite the challenges posed by RP.

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