Western Graduate&PostdoctoralStudies

Western University
Scholarship@Western

Electronic Thesis and Dissertation Repository

8-21-2017 5:00 PM

Predicting Important Patient-Reported Outcomes for Glaucoma Management: Cross-Sectional Study

Lavanya Uruthiramoorthy, *The University of Western Ontario*

Supervisor: Dr. Monali Malvankar, *The University of Western Ontario*
Co-Supervisor: Dr. Daniel J Lizotte, *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics
© Lavanya Uruthiramoorthy 2017

Follow this and additional works at: https://ir.lib.uwo.ca/etd

 Part of the Clinical Epidemiology Commons, Health Services Research Commons, and the Ophthalmology Commons

Recommended Citation

Uruthiramoorthy, Lavanya, "Predicting Important Patient-Reported Outcomes for Glaucoma Management: Cross-Sectional Study" (2017). *Electronic Thesis and Dissertation Repository*. 4837.
https://ir.lib.uwo.ca/etd/4837

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlswadmin@uwo.ca.

Abstract

Background: Seeking direct patient input to inform health care decision making is vital to maintain and improve quality of life among those with chronic diseases. The initiative to incorporate and understand patient-reported outcomes (PROs) in clinical practice has recently increased in the field of ophthalmology to improve glaucoma management.

Objective: To identify the most important predictor variables for four PROs: social support and community integration, presence of depressive symptoms, vision-related quality of life (VRQoL) and preference-based Health-Related quality of life (HRQoL).

Methods: A cross-sectional study was conducted among glaucoma and glaucoma suspect patients in London, Ontario (n = 250). Data were collected through medical chart reviews and face-to-face interviews. The four PROs were measured using validated tools. Linear, logistic and stepwise regression models, and classification and regression trees were built using candidate variables. Through leave-one-out cross-validation, the predictive performance of each model was assessed with mean absolute error, standard error and standard deviation.

Results: Use of mobility aids, best corrected visual acuity (BCVA), income and living arrangements were common predictor variables identified for VRQoL, and social support and community integration. Use of mobility aids was also identified for the presence of depressive symptoms, and BCVA for preference-based HRQoL.

Conclusion: The identified predictor variables suggest that routinely collected variables in ophthalmic practice alone are not sufficient to understand PROs. Our research study presents evidence that may allow better management of glaucoma through guidance of how to integrate patient-centered approach to care with the traditional clinical approach.

Keywords

Glaucoma, patient-reported outcome, social support, community integration, depressive symptoms, vision-related quality of life, preference-based health-related quality of life

Co-Authorship Statement

All chapters of this thesis were written by myself, Lavanya Uruthiramoorthy, to partially fulfill the requirements of the degree of Master of Science in Epidemiology and Biostatistics. Our research project was funded by the Strategic Research Fund (SRF), Lawson Health Research Institute in London, Ontario (July 2015 – July 2017), Principal Investigator: Dr. Cindy M.L. Hutnik, Co-Investigator: Dr. Monali Malvankar. I was involved in all aspects of the study start-up and completion, including: development of the data collection tool and research objectives, patient recruitment, data collection, data entry, data analysis and creating summary reports. My thesis supervisors, Dr. Daniel J. Lizotte and Dr. Monali Malvankar, provided guidance and valuable feedback throughout the entire process. Feedback on the thesis was also provided by Dr. Kathy Nixon Speechley and Dr. Cindy M.L. Hutnik.

Dedication

I would like to dedicate my thesis to my beloved parents, without whom none of my success would be possible. I am forever grateful for their unconditional love and support.

Acknowledgments

I would like to begin by expressing my sincere gratitude and appreciation for the support and guidance of both my supervisors, Dr. Daniel J. Lizotte and Dr. Monali Malvankar. They have provided me with encouragement and compassion during this journey. Dr. Daniel J. Lizotte's expert advice was critical to forming the basis of my statistical analysis. I am thankful for his willingness to assist me during the hurdles of this thesis.

I would like to express my gratefulness to Dr. Cindy M.L. Hutnik, who provided me with valuable clinical insight and guidance for my thesis. She has been a great mentor and inspiration over the past few years. I am thankful for her support and motivation from the start to the completion of my thesis. Furthermore, I would like to thank Dr. Kathy Nixon Speechley for her insight, assistance and critical appraisal of my thesis. Her comments allowed me to take on a different perspective and was a significant contribution to enhancing the overall quality of my thesis.

Moreover, I would like to thank my family and friends for their endless support and love. I would also like to thank all the patients who took their time to participate in this study and share their stories –it was an enlightening experience.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ACG	Angle Closure Glaucoma
ADVS	Activities of Daily Vision Scale
BCVA	Best Corrected Visual Acuity
CCT	Central Corneal Thickness
CDR	Cup-to-Disc Ratio
CERSI	Centers of Excellence in Regulatory Science and Innovation
CIGTS	Collaborative Initial Glaucoma Treatment Study
CIQ	Community Integration Questionnaire
dB	decibels
EQ-5D	EuroQoL - 5D
FDA	Food and Drug Administration
HAM-D	Hamilton Depression Rating Scale
HRQoL	Health-Related Quality of Life
HRT	Heidelberg Retinal Tomography
ICF	International Classification and Functioning, Disability and Health
IOP	Intraocular Pressure
MAE	Mean Absolute Error
MAR	Missing at Random
MCAR	Missing Completely at Random

MNAR	Missing Not at Random
MSE	Mean Standard Error
MD	Mean Deviation
NEI VFQ-25	National Eye Institute Visual Function Questionnaire - 25
NTG	Normal Tension Glaucoma
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
PHQ-9	Patient Health Questionnaire - 9
POAG	Primary Open Angle Glaucoma
PRO	Patient-reported Outcome
QoL	Quality of Life
RMSE	Root-Mean-Square Error
RNFL	Retinal Nerve Fiber Layer
SIP	Sickness Impact Factor
SF-36	Short Form Survey - 36
TTO	Time Trade-Off
VA	Visual Acuity
VAQ	Visual Activities Questionnaire
VF	Visual Field

VF-14	Visual Function Index
VRQoL	Vision-Related Quality of Life
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life

Chapter 1

1 Introduction

Glaucoma is a disease of the nerve that connects the eye to the brain. It is the most common cause of irreversible blindness worldwide and its cause remains unknown[1]. In 2002, glaucoma accounted for about 12.3% of the 37 million people who were blind world-wide[2]. Vision loss is the most frequently feared disability for Canadians and has one of the highest direct health care costs[3]. Globally, the direct cost of vision loss in 2010 was $2.3 trillion[4]. In the United States, it was estimated that 17.8%, of the direct costs from ocular diseases, was due to patients with glaucoma[2]. In 2007, the financial burden of vision loss in Canada was estimated to be $15.8 billion and by 2032, vision loss is expected to cost Canadians about $30.3 billion [3].

Public spending on healthcare is one of the largest government expenditures and health care costs continue to escalate, especially with the elderly Canadian population expected to represent about 25% of the population by 2036[5]. Given the cost constraints, policy decisions to deliver quality health care, optimal clinical practice and a patient-centered health care system must be supported by evidence that incorporates patient-reported outcomes (PROs)[6]. The diagnosis and progression of glaucoma is accompanied by negative consequences on health outcomes directly affecting the patient[7]. Thus, in addition to clinical characteristics of glaucoma, expanded elements of health care such as the economic burden, patient characteristics and PROs also need to be measured for glaucoma management.

Although glaucoma cannot be cured, the progression can be delayed with treatment. Glaucoma impacts the patient in various ways, such as psychological effects, functional disabilities, treatment side effects, treatment costs, and inconvenience of treatments[8]. In today's healthcare climate, patients with glaucoma need to be managed efficiently in a comprehensive manner, rather than a limited scope determined solely by the clinical symptoms of the eye. Quaranta et al. (2016) presented a review of the quality of life (QoL) literature in glaucoma, which suggested that patients with glaucoma may be at a higher risk for a lower QoL, including the burden from side effects and costs of treatment[9]. Since, glaucoma is a multifactorial disease and requires multidimensional management, understanding the factors associated with different QoL domains

is necessary for developing effective interventions[10]. Current treatment options for glaucoma include topical and oral ophthalmic medications, laser and incisional surgical treatments, all which focus on prevention of disease progression by reducing intraocular pressure (IOP)[9]. Some patients may not require initiation of treatment upon first assessment, but rather may be routinely observed until the risk of progression is sufficient to warrant intervention. The primary goal is to preserve the patients' QoL by preventing functional visual impairment and minimizing the side effects and complications of glaucoma treatment[9]. Thus, analyzing the relationship between clinical characteristics, individual characteristics and various QoL domains will provide a more comprehensive understanding of the patient to assist with glaucoma management. Glaucoma management entails more than just the correct diagnosis of the disease, because it requires lifelong treatment and assessment[11]. To effectively treat and manage the patient, a comprehensive understanding of the patient is required. This will allow for patients to be more involved in their care, understand the disease progression, improve their overall health and reduce avoidable health care costs[11].

In ophthalmic practice, disease management outcomes have been mainly assessed with clinical characteristics as opposed to PRO measures[12]. Over the recent years, the need to understand the fundamental disease processes, appreciate individual differences, preserve high level of visual function while improving the quality of care has enticed tremendous interest in studying PROs among glaucoma patients[9,13–18]. PROs are fundamental to involving patients in their clinical decision-making process and understanding patient experiences, as we move from a "disease-based" to "patient-centered" model of care[12,13]. This is especially important in chronic diseases that require compliance to lifelong management. Linking clinical and demographic variables to PROs is important for understanding the associations between variables within a complex construct such as Health-Related quality of life (HRQoL). Understanding this association is important to describe the patient's experiences in response to their disease management and treatment. Overall, it is an improved method of assessing the patients' health status[19]. Thus, in addition to expert opinions and review of relevant literature, this thesis presents the adaptation of a model that conceptualizes the associations of clinical variables to HRQoL measures, proposed by Wilson and Cleary in 1995 (Figures 2-1 and 2-2)[19].

Improving health among glaucoma patients starts with understanding health outcomes as perceived by the patient (i.e., PROs). The importance has recently increased due to the creation of formalized programs by governments which seek direct patient input into health care decision making policies – Food and Drug Administration (FDA) and Centers of Excellence in Regulatory Science and Innovation (CERSI) project[20], and Ontario Clinical Expert Panel for the Glaucoma Quality Standard (May 2017). While the need to integrate PROs in glaucoma management and treatment is apparent, it is routinely not used by ophthalmologists[21]. The "Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye" does not specify the PRO instruments available, thus ophthalmologists may not be aware of which instruments are relevant to their patients [22]. There are several instruments available to assess PROs, therefore determining which one to use among glaucoma patients can be a challenge.

Developing a predictive model for PROs may improve clinical decision-making by providing guidance as to how to incorporate PROs in ophthalmic practice and identifying the need for additional support and/or resources. Machine learning techniques are used to automatically detect patterns from a given dataset and in the clinical decision-making process[23]. Previous studies of glaucoma have not performed machine learning techniques to identify which variables are predictive of PROs. The first step to building a predictive model, is to identify important clinical and demographic variables that are strongly associated with a specific PRO. This is the goal of our research study. The identified clinical and demographic variables will be used to build a predictive model aimed to estimate PROs. The developed model can be used to identify patients at risk of poor PROs and determine clinical interventions as per the patients' needs. This resulting predictive model will further need to be assessed for accuracy in various populations in order to be used as a validated tool. The predictive model can also be beneficial for research purposes, as it will allow researchers, health economists, policy makers and health care administrators to efficiently estimate PROs at a population level to provide evidence to guide administrators on health budget allocation for chronic diseases such as glaucoma.

Chapter 2

2 Literature Review

2.1 Background of Glaucoma

Population based studies identified glaucoma as the main cause of irreversible world-wide blindness[24]. Glaucoma is a chronic neuro-degenerative disorder of the optic nerve that is characterized by progressive structural and functional loss, resulting in vision loss and blindness[24,25]. It is characterized by the degeneration of retinal ganglion cells and their axons, which results in visual impairment and optic nerve damage [26]. Retinal ganglion cells receive visual information and the optic nerve is responsible for carrying the visual information from the eye to the brain[26]. Retinal ganglion cell death and optic nerve fiber loss are among the most important changes that characterize the glaucoma diagnosis[27]. Initial changes to the optic nerve are asymptomatic[28].

Glaucoma is detected through a comprehensive eye examination that includes assessment of the status of the optic nerve and retina, measurement of the best corrected visual acuity (BCVA) at various distances, intraocular pressure (IOP), central corneal thickness (CCT), visual field and assessment of the anatomical angle between the cornea and iris[29]. Some of the major risk factors for glaucoma that have been identified include: elevated IOP, increased cup-to-disc ratio (CDR), decreased CCT, pseudoexfoliation syndrome, genetic factors and older age[24]. IOP is the only currently known treatable risk factor, which is reduced using medication, laser and/or traditional surgery[30]. There are also potential risk factors that remain unidentified.

In a healthy eye, constant eye pressure is maintained, whereas in an eye with glaucoma the damage occurs when fluid builds up and increases the pressure in the eye[31]. There is a subset of patients who experience glaucomatous optic neuropathy at normal IOPs which further highlights the complexity of the disease and likely contributes to the fact that the etiology remains unknown[32]. Glaucoma patients begin losing their peripheral vision which progresses to central visual loss followed by blindness if left untreated. Most glaucoma diagnoses are based on progressive structural and functional optic nerve damage; however there is currently no definitive standard for diagnosis[31]. Since glaucoma is not curable and is irreversible, the goal of

glaucoma management and treatment is to minimize its progression and to preserve the patients' HRQoL. Glaucoma treatment starts with establishing the type of glaucoma diagnosis[33].

2.2 Types of Glaucoma

There are several types of glaucoma that have been identified based on etiology of the underlying disease and mechanism of abnormality in the eye. The two main types of glaucoma include open-angle and angle-closure.

Primary Open-angle glaucoma (POAG) is the most common type of glaucoma characterized by a functional blockage of the drainage canal[34,35]. Because of the blockage, fluid accumulates and causes increased pressure in the eye and damage to the optic nerve.

Angle-closure glaucoma (ACG) requires immediate medical attention when it occurs acutely, because the entrance to the drainage canal becomes anatomically very narrow or completely closed[35]. Thus, the pressure can rise rapidly and cause extreme pain to the patient and sudden vision loss.

Normal tension glaucoma (NTG) is a type of glaucoma in which the optic nerve is damaged without increased pressure in the eye[34]. It is unclear as to why the optic nerve is susceptible to damage, even when the eye pressure is relatively normal.

Secondary glaucoma develops secondary to other conditions such as diabetes, eye trauma or inflammation in the eye, in which the additional factor causes elevated IOP[34]. The most common types of secondary glaucoma include: pseudoexfoliative glaucoma, pigmentary glaucoma and neovascular glaucoma.

Glaucoma suspects are patients who have some, but not all, of the featured characteristics of glaucoma. Glaucoma suspects may have normal pressure in the eye, but their optic nerve or visual field findings suggest a risk of developing glaucoma[34]. In some cases, patients may have elevated eye pressure (ocular hypertension) but show no signs of optical nerve damage. Patients with ocular hypertension are at greater risk for developing glaucoma compared to age-matched normal subjects[34]. Glaucoma suspects can be those

that have risk factors for future development of glaucoma or those who suffer early glaucoma damage that cannot be differentiated from normal damage due to aging[36]. Depending upon the extent of the risk factor profile, glaucoma suspects may or may not receive treatment.

2.3 Epidemiology of Glaucoma

2.3.1 Prevalence of Glaucoma

Most of the epidemiological studies in glaucoma pertain specifically to POAG, because most studies were conducted in North America and Europe, where the most common form of glaucoma is POAG[37]. Several studies have attempted to determine the prevalence of glaucoma since the 1920s, however the criteria for diagnosing glaucoma have changed since then and continue to evolve, the latter primarily based on advancements in diagnostic technologies[38–40]. It was not until 1938, when gonioscopy was introduced, that open-angle and closed-angle glaucoma were differentiated and glaucoma was not merely based upon the elevation of IOP[38].

Glaucoma is the second leading causes of global blindness and the leading cause of irreversible visual loss that disproportionately affects people residing in Asia and Africa[2,41]. In 2010, it was estimated that about 60.5 million people globally were affected by glaucoma and this number is expected to increase to 79.6 million by 2020 and 111.8 million by 2040[41,42]. Data from population based studies reported the mean prevalence for POAG worldwide in 2010 as 1.96% and 59.1% of all people with glaucoma were female[42]. Although there have been a number of prevalence surveys conducted in various racial and ethnic groups worldwide, caution must be taken in interpreting these results as there exists great variability in the methodology, quality of the data collected and variability among glaucoma diagnostic criteria[43].

POAG is the most common form of glaucoma, accounting for about 19% of all blindness among African Americans compared to only 6% of Caucasians[44]. Africans have a higher prevalence of POAG than do Europeans or Asians, and ACG is most common in Asians[38,43]. African Americans are 15 times more likely to be visually impaired and six to eight times more likely to be blind from glaucoma than Caucasians[45]. In a systematic review and meta-analysis that included population-based studies published up until March 2013, the global prevalence of

glaucoma was reported to be 3.54% for a population between 40 to 80 years of age[41]. Prevalence increases proportionally with age. Those older than 70 years of age have an "average estimated prevalence of 6% in white populations, 16% in black populations and 3% in Asian populations"[38]. Thus, glaucoma is of great concern due to the current aging population. It is also important to note that the rate of undiagnosed glaucoma is fairly high, since glaucoma is often asymptomatic until the very advanced stage at which point irreversible functional blindness is likely[41].

Population based studies for determining disease prevalence are crucial, since there exist regional differences in the prevalence of different types of glaucoma[46]. However, such studies are minimal in Canada. In 1965, a screening survey of about 18,000 participants conducted in Scarborough, Ontario reported a glaucoma prevalence of 2.2%[47]. Analysis of self-reported data in 2002 to 2003, revealed that about 409 000 Canadians were diagnosed with glaucoma, of which 2.7% were above 40 years old and 11% were above 80 years old[26]. Then in 2005, another screening study on a high-risk population reported glaucoma in 7.2% of the participants[49]. In 2007, based on Canada-wide health surveys, the prevalence of self-reported glaucoma was 2.7% among Canadians older than 40 years of age[50]. Further, in a 2008-2009 cross-sectional study conducted in Toronto, Ontario consisting of Canadians 50 years of age or older, reported 7.5% of the participants having glaucoma and the prevalence of undetected glaucoma was 3.9%[50]. It is estimated that about 50% of people with glaucoma are not aware that they have the disease and therefore are not receiving glaucoma treatment[51]. Since glaucoma is relatively asymptomatic in the early stages, the statistics obtained from health surveys are likely underestimated.

2.3.2 Incidence of Glaucoma

Very few incidence studies of glaucoma have been reported. Since POAG is initially an asymptomatic disease, patients may not seek treatment until the later stages. Effective screening for glaucoma continues to be a global health problem[52]. In the earlier stages, it can be challenging to identify the precise stage at which a glaucoma suspect progresses to glaucoma. Difficulties with staging the glaucoma diagnosis and the need to follow up with patients is a challenge in determining the incidence of glaucoma[37].

The first reliable data were collected in a 1989 longitudinal study, in Sweden, among a population of 55 to 69 years of age, which reported the estimated incidence rate to be 0.25% in a 10 year follow-up period [28]. In a more recent study the four-year incidence of POAG in Barbados was reported to be 2.2%, and incidence rates increased from 1.2% at 40 to 49 years of age to 4.2% at 70 years or greater[38]. Among people in Netherlands, the rates increased from 1% at age 60 to 3% at age 80[38]. The incidence rate over time in a Caucasian population increased from 0.08 at 40 years of age to 1.46 at 80 years of age[37]. Thus, the incidence of glaucoma increases with age.

2.3.3 Risk Factors for Developing Glaucoma

When assessing the risk factors for a disease, large population-based studies are more representative than hospital-based studies, due to the selection bias among hospital patients, which can lead to an overestimation of certain potential risk factors for developing glaucoma[37]. The main risk factors that have been examined in population-based studies include: demographic factors such as age, gender and race; ocular factors such as IOP, appearance of the optic nerve, myopia, hypermetropia, presence of exfoliation, pigment dispersion, inflammation, narrow angles and history of trauma; systemic factors such as diabetes, hypertension and vasospastic disorder; genetic factors and other proposed lifestyle risk factors such as cigarette smoking and alcohol intake[37].

2.4 Glaucoma Treatment and Management

There is always a trade-off involved when making treatment decisions. In the case of glaucoma treatment, patients make a treatment decision based on the trade-off between avoidance of blindness and treatment side effects and complications[53]. Understanding HRQoL in glaucoma patients could provide insight into the extent of visual disability and side effects of the treatments from the perspective of the patient[9]. It is both ideal and important to consider the patient's perspective and their priorities when developing a treatment plan[27]. This is further punctuated by the fact that glaucoma management has been plagued by well documented poor patient compliance to medical therapy[11,54,55]. Since glaucoma is a progressive disease and is incurable, understanding how glaucoma affects PROs can influence medical decision making to optimize

treatment strategies and adherence, develop rehabilitation programs, allocate necessary resources and ultimately improve patient-physician relationships[7].

Glaucoma treatments include medications, laser and surgical interventions, which can influence the patient's HRQoL, by relieving symptoms but also by inducing side-effects and complications. As POAG tends to be asymptomatic in the early to moderate stages, patients often perceive the treatments as being more negative than the disease itself. In a cross-sectional study among POAG and ocular hypertension (OHT) patients, in addition to clinical characteristics, medication side effects and glaucoma surgery also affected HRQoL[56]. Commonly reported side effects from topical and systemic medications include burning, tearing, blurred vision, stinging and redness[57]. In addition, the complexity of treatment regimen; taking multiple doses; having to travel with the medications; and difficulties in administering medications can negatively influence HRQoL[57–59]. In a cross-sectional study, the results showed that difficulty with the use of medication was the only factor that was negatively associated with HRQoL scores[59]. Other studies have indicated that the greater number of doses per day and use of additional medications correlated with noncompliance[57,59,60]. The daily use of medication may stress the burden of having an incurable disease and interfere with their daily life. Patients who are satisfied with their treatment have a greater adherence to their treatment, more likely to be involved in their care and use resources appropriately[58,59]. Thygesen et al. (2008) reported that the treatment with greater cost savings was found in the social care sector (i.e., assistance with daily activities) as opposed to the health care sector (i.e., medical treatment)[61]. Majority of the costs in terms of glaucoma management were found to be medication-related, with the financial burden increasing with advanced glaucoma severity[62].

The Collaborative Initial Glaucoma Treatment Study (CIGTS) randomized newly diagnosed POAG patients to treatment with medications or trabeculectomy. Although there were very few between-group differences in outcomes, patients in the trabeculectomy group reported more difficulties with visual acuity related activities[58]. After the five-year follow-up period, patients reported a reduction of symptom frequency and burden in both treatment groups[58]. A cross-sectional study with Brazilian glaucoma patients found that surgery was a predictor of poor HRQoL scores in patients only with early stage glaucoma[60]. A cross-sectional study investigating the HRQoL among three groups: medical treatment, surgical treatment and

combination of medical and surgical treatment found no difference between the HRQoL scores among patients in the surgical or medical group[60]. The results also suggest that in the surgical group, glaucoma had less of an impact on their daily lives, although patients were still concerned about the progression of glaucoma[60].

Glaucoma is a chronic disease that affects many aspects of a patient's life; thus, success of glaucoma management should not be measured only by objective clinical parameters such as IOP. This is a key factor when considering the goal of the various therapies. For example, a low risk surgical intervention that reduces the dependency on medications may be far more beneficial to a patient's QoL without any additional effects on IOP reduction. Many patients with glaucoma are combating other concurrent comorbidities requiring treatment that could influence their compliance and satisfaction.

Optimal treatment and management should incorporate objective measures of the patient's visual function and glaucoma severity, as well as the subjective measure of the likely PROs under different possible treatment options[63]. In terms of a cost-effective treatment, the goal is to achieve a better health outcome at a lower cost. Thus, understanding the impact of glaucoma, identifying individual needs and assessing the effectiveness of treatment options is crucial to glaucoma management.

2.5 Health Outcomes of Glaucoma

Traditionally, health outcomes were based on a biomedical model and objectively defined as mortality and morbidity associated with biological functioning[13]. This approach does not consider the patients' perception and experiences of their current health state. More recently, health outcomes are being viewed in terms of a biopsychosocial model, which incorporates a more holistic view of the patient and includes psychological and social factors[64]. Health outcomes discussed in our research study include clinical outcomes and PROs.

2.5.1 Clinical Outcomes

Clinical outcomes are outcomes that are not reported by the patient and are used by clinicians to diagnose and manage the progression of the disease[13]. There is great variability in the clinical presentation of patients with glaucoma[27]. Clinical outcomes are identified through a

comprehensive eye exam which include the following assessments: best corrected visual acuity (BCVA), gonioscopy, tonometry, corneal pachymetry, perimetry, visual acuity test and optic nerve and retinal nerve fiber layer imaging [65]. All components of the eye exam are used to diagnosis and determine the staging of glaucoma (Section 4.4.2.5 defines the stages of glaucoma). Clinical outcomes vary depending on the type and severity of glaucoma[30].

2.5.1.1 Gonioscopy

Gonioscopy is a technique used to assess the configuration of the anterior segment angle. This is located between the cornea and the iris[66]. Goinioscopy permits the determination of whether the angle is anatomically open or closed[66].

2.5.1.2 Tonometry

Tonometry measures the IOP using a tonometer[27]. Although, elevated IOP levels is a prominent clinical presentation that is strongly associated with the development of glaucoma, there are patients with elevated IOP levels (> 21 mm Hg) that do not develop glaucoma and other patients who are diagnosed with glaucoma who have a normal IOP level (≤ 21 mm Hg)[26,67].

2.5.1.3 Corneal Pachymetry

Pachymetry determines the corneal thickness. Normal CCT ranges between 545 and 550 μm and is race dependent[66]. Thin corneas (< 500 μm) are a risk factor for progression of glaucoma, while thicker corneas (> 600 μm) are relatively protective[30].

2.5.1.4 Perimetry

A perimetric test, also known as visual field test, is used to quantify the level and rate of functional visual impairment and is complemented by image-based structural measurements of the optic disc, retinal nerve fiber layer and ganglion cells[68]. Visual field loss is a sign of glaucomatous damage and is a crucial measurement for management of the disease[68]. Mean deviation (MD) is the overall deviation from normal values (0 dB to -2 dB) of the hill of vision which defines the visual field[69].

Glaucoma at a later stage is generally more straightforward to diagnosis; however for glaucoma suspects, who present with normal visual field and elevated IOP, they usually require repeat perimetric tests over time[68]. With patients already diagnosed with glaucoma, perimetric tests play a key role in managing the disease to determine if the treatment is adequate or if a change is required[68].

2.5.1.5 Visual Acuity Test

The Snellen chart is an eye chart typically used to measure central visual acuity, which is a measure of how well a patient sees at various distances (i.e., sharpness of vision)[27]. Visual acuity is scored as a set of two numbers known as the Snellen fraction[70]. For example, usually 20/20 is defined as normal, where the top number represents the distance from which the test is conducted and the bottom number represents the distance that the typical healthy eye can see the letters on a certain line of the eye chart[70]. The loss or abnormality of visual functions leads to visual impairment[71].

2.5.1.6 Optic Nerve and Retinal Nerve Fiber Layer Imaging

Dilated eye examination is performed to examine the optic nerve and retina for signs of damage[66]. Specifically, the imaging tests used are Heidelberg Retinal Tomography (HRT), which provides a quantitative evaluation of the topography of the optic nerve and/or Optical Coherence Tomography (OCT) which measures the retinal nerve fiber thickness within the retina[72].

Optic nerve damage produces thinning and decreased visibility of the retinal fiber layer (RNFL) [35]. Due to the way the retinal ganglion cells enter the optic nerve, the vertical cup-to-disc ratio is a useful clinical measurement of the structural status of the optic nerve[30]. Typically, glaucoma is associated with a progressively increasing cup-to-disc ratio, due to the degeneration of the retinal ganglion cells[30]. Normal cup-to-disc ratio is about 0.3 (ranging between 0.1 and 0.8)[67].

2.5.2 Symptoms

Symptoms are associated with the disease itself and the treatment effect[73]. Glaucoma progression can be asymptomatic in the early to moderate stages of the open angle disease[27]. Elevated IOP usually raises concern about the risk of glaucoma[69]. Pain is experienced by the patient when IOP

rises rapidly[69]. Visual impairment is the most noticeable symptom of glaucoma, but this is typically not experienced by the patient until the later stages of the disease[69]. Glaucoma usually develops slowly with very minimal initial symptoms; however, in some patients the rate of loss can be relatively rapid, depending upon several factors including the stage of the disease at the time of diagnosis[74]. Thus, it is important to routinely examine glaucoma suspects on a regular basis[66]. A key point is that the damage is irreversible with no known treatments once it has occurred.

2.5.3 Patient-Reported Outcomes

Clinical characteristics such as visual field and IOP are predominately the main outcomes assessed for clinical and research purposes despite neither defining the disease. As these are not able to provide information on the well-being and experiences of the patient, there is a need to focus on assessing PROs. Patients with glaucoma experience visual impairment, activity limitations, side effects of treatment, as well as effects on general health, lifestyle and emotional well-being. In addition to the medical problem, these patients experience social, economic and psychological problems. Thus, multidisciplinary approaches to research are needed to understand the biological, psychological and sociological factors influencing health-related outcomes as perceived by the patient. Understanding how glaucoma affects the patients' daily activities as well as obtaining a perspective on the effects of disease progression and treatment are important in a patient-centered comprehensive approach to glaucoma management.

PROs are needed to assess health outcomes from the patients' perspective. PROs are able to address the patients' vision-specific functional loss affecting different domains of their life and overall satisfaction of the patient's health state[23]. PROs are subjective measures reflecting patient experiences, perceptions, symptoms, functional status or other domains influencing HRQoL, in terms of their health condition[75]. PROs represent what is important to the patient as it relates to the management and treatment of the disease[75]. Hence, PROs can help improve patient knowledge, identify issues and provide insights that influence glaucoma management[76].

2.5.3.1 Quality of Life and Health-Related Quality of Life

QoL and HRQoL are generic health outcome measures, which are often used interchangeably. Although QoL and HRQoL capture the subjective health perception of the patient, they each provide different information[77]. QoL is defined as a broad concept which encompasses all aspects of life such as family circumstances, finance, living arrangement and job satisfaction[77]. QoL is defined in the context of the patients' culture and values[76]. On the other hand, HRQoL is a component of QoL that is focused on the individuals' perspective of their own health state as it relates to their overall functioning and well-being in terms of physical function, social and psychological factors[77]. HRQoL is usually a measure of self-perceived health status, depicting how health affects QoL or the utility associated with different health states[77].

Although the ocular damage due to glaucoma is initially asymptomatic, the patients' HRQoL can be affected as soon as the diagnosis is made and/or the early damage and its treatment cause effects other than diminished central acuity. One of the very first studies to understand HRQoL in glaucoma patients in 1997, found that visual function impairment was correlated with peripheral vision, distance activities and vision-specific dependency[78]. Research across different HRQoL domains is important in order to provide insight to the aspects of daily living that are negatively affected by glaucoma[76]. Poor HRQoL in glaucoma patients can be due to various reasons and can differ across various patient populations. Reasons for diminished HRQoL specifically among glaucoma patients include: stress of diagnosis, disease severity, functional loss due to vision loss, loss of independence, inconvenience of frequent treatment and its side effects, cost of treatment and regular appointments for monitoring the progression of glaucoma[62]. Literature supports that even the mere diagnosis of glaucoma can negatively affect HRQoL[79]. Glaucoma is a progressive disease, but the diagnosis of glaucoma can come as a surprise to many patients, since patients may attribute their vision loss to normal degradation with aging[29]. It is often shocking to patients that they already have moderate to advanced disease at the time of diagnosis[80,81]. Current literature suggests HRQoL is more affected by the way patients perceive their vision as opposed to the objective measurement of it[9].

Patients diagnosed with POAG reported lower HRQoL scores than patients with suspected glaucoma[9]. Another study which used the same HRQoL measure, but with a larger proportion of

patients with early stage glaucoma, reported that HRQoL scores were not greatly affected by visual acuity or visual function impairment[9]. Past studies also suggest that HRQoL scores tend to be worse in patients with more advanced stages of glaucoma and with concurrent comorbidities[9,82]. In a cross-sectional study among POAG and OHT patients, the clinical characteristics that affected HRQoL were MD and visual acuity[56]. The findings also suggest a stronger impact of visual function loss in the better eye on HRQoL than visual function loss in the worse eye[9,56]. Evidence in the literature suggests that the worst HRQoL is associated with more severe glaucoma, however there still exists some evidence of worst HRQoL even in the early stages of glaucoma[17]. Generally, HRQoL scores are associated with visual function loss, visual acuity and number of years since glaucoma diagnosis[9]. Despite the variability in study methodology, several studies have reported significant relationships between visual impairment and HRQoL[9,83].

2.5.3.2 Functional Status and Well-being

Health effects of glaucoma extend beyond the eye, as patients with glaucoma experience limitations to their functional status and well-being[84,85]. Clinical outcomes such as visual field and visual acuity loss, can limit the patients' ability to be independent, productive, participate in society, perform daily activities, and impact social and emotional well-being[85]. Assessing functional status and well-being is important to inform rehabilitation care[9].

The World Health Organization (WHO) refers to disability as a broad term encompassing impairments, activity limitations and participation restrictions[86]. Patients with disabilities, such as visual impairment, require coordination of care among a multidisciplinary care team (i.e., optometrists, ophthalmologists, social workers and rehabilitation services). 'Functional status' and 'health status' are among other terms used in a similar context as QoL and HRQoL[13]. Health status is usually referred to the broader well-being of the patients in terms of disability[54]. Functional status assess the ability of the individual to perform social roles without any limitations and focuses on tasks such as activities of daily living[77].

Performing activities of daily living is often a problem in patients with visual impairment[85,87]. Visual impairment and progression to blindness, increases functional disability, dependency, accidents, depression, decline in physical and mental health[9,76,87,88]. Patients with bilateral visual

field loss have reported poor performance on mobility activities such as driving, in comparison to patients with unilateral visual field loss[89]. Progression of glaucoma can lead to vision-related disability, loss of visual acuity and blindness, thus patients experience problems associated with activities of daily living such as reading and driving[24]. Visually impaired individuals are at a higher risk for accidents, social withdrawal and depression[9]. Due to the loss of visual acuity in glaucoma patients, many report concern with activities requiring central and near vision and outdoor mobility[9]. Activities such as walking, reading, visibility at night and noticing objects through peripheral vision, have been reported to be major concerns[45]. Patients with moderate to severe visual field loss, decreased contrast sensitivity and depth perception, report difficulties with driving and the need to discontinue or drive less frequently[9]. Tasks requiring central or near vision, outdoor mobility and driving are the most deteriorated activities of daily living among glaucoma patients[76]. Outdoor mobility restrictions was strongly correlated with the amount of visual field loss in the worse eye and those with visual impairment were more likely to report accidents and falls[76]. Such limitations to activities of daily living can lead to patients' loss of independence and lower HRQoL. Glaucoma patients with moderate to severe visual field loss perform poorly on activities related to functional independence and level of mobility[90].

Glaucoma is a chronic condition that potentially can cause blindness[91]. Patients with glaucoma have reported high prevalence of anxiety and depression[17]. Driving limitations, fear of falling and imbalance also contribute to the relationship between glaucoma and depression[17]. In a case-control study, anxiety and depression in POAG patients was reported to be significantly higher than the reference group[92]. In addition, increase in age and visual field loss were associated with depression[92]. Symptoms of depression were not found to be correlated with poor visual function; however, it was significantly correlated with the patient's perception of their vision[92].

Glaucoma impacts a patient's everyday functional abilities and each patient copes with the disease differently[85]. Understanding how glaucoma impacts the patient's functional status and well-being, can assist with developing better management strategies for patients with glaucoma.

2.6 Patient-Reported Outcome Instruments

PRO instruments measure the patient's health status such as HRQoL[6]. They are often self-reported by the patient, but can also be completed by a proxy if the patient cannot self-report.

Assessing PROs to better manage the patient can be difficult using only one instrument, since patient tailored care requires a multidimensional understanding: personal factors, social relationships and participation, psychological well-being, physical health and health condition[73]. Although PROs are considered an important aspect of the patient's health management and is collected in a standardized method in certain clinical practices, they are rarely collected in ophthalmic practice due to possible reasons such as: determining which PRO measure to use; lack of guidance on how to implement PRO measures routinely; difficulties with interpreting the results; time constraints; and resource limitations[63,73,93]. Currently, there is a priority to incorporate the collection of PROs in ophthalmic practice, and a group of ophthalmology experts in Ontario are making an effort with government professionals to implement PRO assessment in routine practice –Ontario Clinical Expert Panel for the Glaucoma Quality Standard, 2017. Types of developed PRO instruments include: generic, disease-specific, dimension-specific and utility measures[88].

Among patients with glaucoma or at risk of glaucoma, previous studies assessed PROs using generic, glaucoma-specific, vision-specific, medication-specific and utility instruments[95–97]. These studies often used a combination of one generic and one vision-specific instrument. Our research study uses four different PRO instruments. There is a need for clear recommendations and guidance in clinical utilization of PRO instruments, given the plethora of PRO instruments available.

2.6.1 Generic Instruments

Generic tools were developed to provide the overall impact of the health condition and can be compared across various health conditions and are used to measure the general functional status of the patient [98]. Among generic instruments such as: EuroQol-5D (EQ-5D), the Sickness Impact Profile (SIP) and World Health Organization Quality of Life (WHOQOL), the most common generic tool used in glaucoma research is the Medical Outcomes Study Short Form-36 (SF-36)[17].

The main advantage with the generic tool is that it can be used to compare across various populations, including populations without the health condition of interest[13]. These instruments provide a summary score across various dimensions such as physical and social functioning,

emotional and physical problems, role limitations and mental health[13]. However, because generic instruments assess broad dimensions, they may not be as directly relevant to specific populations and are potentially less responsive to clinically important changes[13]. Studies using the generic instrument found that patients with glaucoma reported lower scores across all domains, compared to patients without glaucoma[85,99].

2.6.2 Glaucoma - Specific Instruments

Glaucoma-specific instruments focus on the specific disease and reflects issues that are important to patients with glaucoma[97]. They are usually used to detect changes in the same population over time[97]. Glaucoma-specific tools assess the symptoms, functional impairment, vision-related factors and extent to which glaucoma and treatment interfere with their health state[94]. They are clinically relevant, specific to the disease, but are rarely used in clinic, rather are mainly used as a research tool[94]. Overall, disease-specific instruments are more relevant and sensitive than generic instruments with regards to capturing changes in health status due to glaucoma management and treatment[94].

2.6.3 Vision - Specific Instruments

Vision-specific instruments measure the functional impairment among patients with ocular conditions. They focus on visual ability, specific task performance and impact of visual impairment on the patient and their daily acitivites[98]. Commonly used vision-specific instruments include: the Visual Function Index (VF-14), National Eye Institute Visual Function Questionnaire (NEI VFQ), Activities of Daily Visual Scale (ADVS) and Visual Activities Questionnaire (VAQ)[98]. Vision-specific instruments were reported to be more sensitive than generic instruments when comparing patient with glaucoma to a reference group[46,72,73]. They were also found to be more correlated with clinical assessments[46,72,73].

2.6.4 Dimension - Specific Instruments

Dimension-specific instruments are not popularly used in glaucoma research, thus their appropriateness as an outcome measure needs to be carefully considered and data on their psychometric properties are limited. Dimension-specific instruments are used when there is an interest in assessing a specific domain (i.e., social and emotional well-being). It is often more

detailed than the generic and disease-specific instruments[13]. Dimension-specific instruments discussed in this project include the Community Integration Questionnaire (CIQ) and the Patient Health Questionnaire - 9 (PHQ-9).

2.6.5 Utility Measures

Utility measures provide information on the patient's preferences and values as it relates to their current health state[13]. Generally used techniques to obtain direct health utility values include: rating scales, standard gamble and time trade-off[13]. Utility values are useful for economic evaluations such as cost-utility analysis[13].

2.7 Selected Patient-Reported Outcomes

Selection of appropriate PRO instruments depends on the purpose of the study and requires careful consideration of methodological issues such as: validity, reliability, feasibility and generalizability[6,94]. Several PRO tools in glaucoma have been developed to assess aspects of HRQoL. However, the challenge is deciding which of the many measurement tools to use. It is a constant battle to choose a tool that is responsive and relevant to clinical outcomes, and is concise and easy to administer[6]. The responsiveness of the instrument is an important consideration, because the instrument may fail to detect a change which can result in false-negatives[75]. The reliability and validity of these measurement tools are assessed using psychometric properties[100].

Vandenbroeck et al. (2011) conducted a systematic review to identify glaucoma-specific and vision-related functional status, disease specific, treatment specific, and overall QoL tools, based on FDA guidelines[63]. Vision-specific tools are useful to clinicians and are specific to the disease progression and treatments[94]. The disease-specific tools do not capture the multi-dimensional concept that QoL entails[58].

Selecting an instrument to measure PROs depends on the objectives and population under investigation[97]. Based on the literature, time constraints, ease of use, professional judgement, relevance to the study population and study outcomes, the following four PROs were assessed in our research study: social support and community integration as measured by the Community Integration Questionnaire (CIQ); depressive symptoms as measured by the Patient Health

Questionanire-9 (PHQ-9), vision-related quality of life (VRQoL) as measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25); and preference based HRQoL as measured by the Time Trade-Off (TTO) technique.

2.7.1 Social Support and Community Integration

More people are living with disabilities and therefore, there needs to be an emphasis on the inclusion of social well-being to assist patients in rehabilitative strategies. Among patients with visual impairment, functional activities and participation in household, social and occupational activities are important outcome measures[101].

Previous literature identified that an essential component of functional independence and accessibility is being able to drive, and vision-related diseases may prevent individuals from driving. It has been found that individuals with visual impairment have a decrease in functional independence, since they are prevented from performing activities such as driving[102]. Since glaucoma is a disease that causes visual impairment, it influences the patients' driving abilities, and it has been shown that non-drivers have poorer community integration than drivers[103]. Thus, it is important to be aware of these patients' social support and level of community integration, as this can provide support for better tailored interventions. In many other chronic disease populations, such tailored interventions support improvements in QoL[104].

Among other chronic disease populations, social support and community integration has been shown to affect mortality and predict self-reported disease outcomes[104]. Although, there are many instruments available to assess functional abilities, not many assess community integration as a multidimensional concept. The 32-item Craig Handicap Assessment and Reporting Technique (CHART) is the most commonly used measure of integration; however, the CIQ is more comprehensible, brief and easy to administer, with good measurement properties (refer to Section 4.5.1 for a detailed description of the CIQ)[105].

The CIQ was originally developed by an expert panel with experience in various aspects of rehabilitation and research for individuals with traumatic brain injury to assess changes in social functioning[106,107]. It focuses on behavioural states rather than emotional states. It consists of three domains that are consistent with the WHO definition of disability: home integration, social

integration and productive activity[101]. Some items measure the frequency of activities performed and other items measure the degree to which assistance is required to perform activities[101]. The International Classification of Functioning, Disability and Health (ICF) framework consists of a functioning and disability domain that includes activity and participation, which coincides with the CIQ items. The CIQ score ranges from 0 to 29 (greater social support and community integration). Previous studies among brain trauma patients reported that age, sex and level of education to have an effect on CIQ scores and females scored higher in the home integration domain whereas males scored higher in the productive activity domain[108]. Previous studies using the CIQ that were comparable to our study population, were conducted among geriatric patients and patients with physical disabilities[101,109].

Overall, the CIQ is interpretable and feasible in assessing the level of social support and community integration. With diseases that result in some form of disability, it is important to consider outcome measures related to social functioning to evaluate quality of care and need for care beyond medical treatment such as rehabilitation care coordination. Although, the CIQ has not been used in patients with ocular diseases such as glaucoma, vision loss is debilitating, thus it is important to consider the social integration of such individuals. Functional activity and participation are important outcomes across all diseases. The CIQ is generally applicable to patients with a disability and has been used in a heterogeneous sample of adult patients with disabilities[101].

2.7.2 Depressive Symptoms

Vision loss can negatively influence the emotional well-being of individuals[78]. More specifically, vision loss is associated with an increased risk of depression[110]. Among glaucoma patients, depression can arise due to fear of potential blindness, burden of treatments and impairments of activities of daily living[16]. There is the well-known social stigma around mental illnesses and ophthalmologists may not be aware of such conditions when treating their patients. There also exists a relationship between QoL and depression[16]. Tastan et al. (2010) found QoL to be negatively associated with depression in Turkish patients with glaucoma[111]. Depression can also results in disability and loss of productivity[112]. Thus, measuring depressive symptoms may

be relevant to the care of patients with glaucoma and other ocular diseases, to provide these patients with the necessary support and resources.

Lim et al. (2016) reported mild to severe depressive symptoms among 30% of glaucoma patients in Singapore, using the Hamilton Depression Rating Scale (HAM-D)[16]. Lim et al. (2016) also found variables such as sex, race, clinical characteristics and average NEI VFQ-25 scores were significantly associated with depressive symptoms[16]. Further, Skalicky et al. (2008) determined that among their study population, depression prevalence increased with glaucoma severity, using the Geriatric Depression Scale-15[113].

The PHQ-9 was developed as a diagnostic tool for depression. It is one of the most common validated tools used to measure depression in research to identify depressive symptoms. It measures the severity of depression into five categories: none, mild, moderate, moderately severe and severe. It is a rapid assessment tool and it scores each of the nine "Diagnostic and Statistical Manual of Mental Disorders, 4th edition" (DSM-IV) criteria. It is a brief standardized valid tool for assessing depressive symptoms. The PHQ-9 was found to support diagnosis made by clinicians and other screening instruments such as the Beck Depression and Anxiety Inventories and the Center for Epidemiologic Studies Depression Scale[114]. Previous research concluding the PHQ-9 as an adequate tool for diagnosing depressive disorders have been conducted in primary care settings[114].

To date, the PHQ-9 was not used in patients with ocular diseases such as glaucoma. Generally, as the PHQ-9 depression severity increased, there was a decrease in functional status, increase in health utilization and decrease in work productivity[115]. Typically, measures of depression have been assessed as part of a larger measurement tool consisting of a broad array of domains, such as the Short Form health survey. However, for our research study, the PHQ-9 was used to capture the specific dimension of emotional well-being.

2.7.3 Vision-related Health-Related Quality of Life

The most widely used instrument in vision-related functioning is the NEI VFQ-25. It was designed specifically for a clinical setting and consists of 12 domains: general health, general vision, visual pain, near activities, distance activities, social functioning, mental health, role

difficulties, dependency, driving, colour vision and peripheral vision[76]. It was developed to measure vision-specific functioning and impact of vision problems on HRQoL for various ocular conditions. Both the 51-item and the shorter 25-item version questionnaires were widely used in different groups of patients and shown to be internally consistent, reproducible and responsive in glaucoma patients[9]. Vision-specific instruments were found to be more sensitive and relevant to glaucoma than generic QoL instruments, as it contains items regarding activities of daily living, social functioning and coping related to vision loss[57]. The NEI VFQ-25 scores have a closer relationship to clinical outcomes, in comparison to generic instruments [95] .

In the Early Manifest Glaucoma Trial, newly diagnosed glaucoma patients were randomized to receive treatment or no initial treatment. Patients scored a high mean composite score of 88.8 out of 100 on the NEI VFQ-25 scale[116]. Although early treatment significantly reduced clinical outcomes of glaucoma progression, it did not affect VRQoL scores[116]. In addition, the NEI VFQ-25 scores were correlated with low visual acuity in the better-seeing eye, worse MD and lens opacities, but no correlation was found with age, sex, IOP, cardiovascular disease or systemic hypertension[116]. In the Los Angeles Latino Eye Study, a correlation was observed between visual field loss and NEI VFQ-25 subscale scores[117]. Findings from previous studies suggest that glaucoma patients with visual field loss report lower VRQoL scores[9,76,117]. In addition, previous studies found the composite NEI VFQ-25 scores of patients with glaucoma to be lower, and lower scores were correlated with more severe visual field defects[118].

As opposed to a generic or glaucoma-specific instrument, a vision-specific instrument was selected for our research study. Patients with glaucoma may present with other concurrent ocular conditions as well, thus our research study included patients diagnosed with various ocular conditions, including glaucoma and glaucoma suspects. A glaucoma-specific instrument would have been too limited and a generic instrument would have been too broad. Hence, a vision-specific instrument was determined to be valid for our study population.

2.7.4 Preference-Based Health-Related Quality of Life

Although non-preference-based measures are useful in identifying declines in visual function, they do not assess how the patient's visual function influences their daily life[119]. Thus, it is

necessary to assess the patients' perception of their own health state. Preference-based HRQoL outcomes use utility values to present the preference values of the patient.

The two most common methods of assessing utility values are the TTO and standard gamble (SG) methods. The TTO technique s a tool used in health economics to help determine HRQoL of patients, where the patient trades the length of life for QoL. In ophthalmology, the utility value is calculated by dividing the number of years a patient is willing to trade for perfect vision by the numbers of years expected to live, subtracted by 1.0[120]. Utility values are rated on scale between death (utility = 0.0) and perfect health (utility = 1.0). On the other hand, with the SG method, the patient is presented with a theoretical treatment and two possible outcomes (treatment works or does not work)[120]. Patients are then asked the percent chance of blindness they are willing to risk before refusing the treatment[120]. The percentage obtained is then subtracted from 1.0 to obtain the SG utility value, which describes how undesirable the patient perceives their present health state (i.e., the more risk the patient is willing to tolerate, the less desirable they perceive their health state)[120]. The TTO technique is easier to administer than the SG method[119].

Utility values were previously used to measure preference-based HRQoL among glaucoma patients. Total visual acuity, visual acuity in the better eye and comorbidity significantly affect utility scores[9]. A study of glaucoma and glaucoma suspect patients, reported on average high TTO utility values of 0.93 and 0.98 respectively (22% glaucoma and 11% glaucoma suspect patients were willing to trade some years of their remaining life expectancy for perfect vision)[119,121]. On the other hand, a study of Indian glaucoma patients reported on average a low TTO utility value of 0.64, representing a poorer preference-based HRQoL[96]. Gupta et al., (2005) found significant associations between TTO utility values and the degree of visual acuity loss and educational status[96]. The utility values were found to be poorly correlated with visual field. Patients who were blind reported a lower average utility value of 0.67, meaning that they were willing to trade more years for perfect vision. Bass et al. (1997) assessed the utility value of patients prior to cataract surgery, and found that TTO utility values were closely related to feelings of depression and difficulties with social interactions more so than clinical meausres[122]. Brown et al. (1999) found that visual loss is associated with a decrease in the patients'

preference-based HRQoL, in which patients with a poor visual acuity value (i.e., counting fingers) were willing to give up more years of their remaining life compared to patients with a better visual acuity (i.e., 20/20)[123]. A study of Chinese patients reported a mean utility value of 0.88, suggesting that most were not willing to trade their remaining years for perfect vision[124]. Aspinall et al. (2008) reported that only 17% of the patients were willing to consider trading their remaining years of life for perfect vision[125].

The TTO technique is a preference-based measure that assesses the subjective impact of diseases on HRQoL and provides information for economic evaluation. It overcomes the limitation of many questionnaires that provide a composite measure, by using preference-based choices to provide a numerical value representing the patients HRQoL[120]. Although utility measures lack precision, unlike other HRQoL measures, they allow for comparison across various disease states[119]. Hence, the TTO technique was used for our research study.

2.8 Linking Clinical Variables with Patient-Reported Outcomes

Health outcomes are influenced by clinical factors, characteristics of the individual and environmental factors (i.e., healthcare facility, social support system). Several different PRO measures are used, which makes it difficult to compare results across studies[126]. In addition to literature review and expert opinions, the Wilson and Cleary (1995) model was adapted to identify variables and outcome measures for our research study.

The Wilson and Cleary (1995) model incorporates biological, social and psychological domains to present the relationships among measures of patient outcomes (Figure 2-1)[19]. The model illustrates that all components lead to an overall HRQoL as the endpoint. However, the purpose of our research study was not to assess overall HRQoL, but rather specific domains of HRQoL. Thus, the model was adapted to fit our research objectives (Figure 2-2). The characteristics of the environment were excluded, since all patients were recruited from the same health care institution and were cared for by the same ophthalmologist. Although the original model developed by Wilson and Cleary (1995) illustrates causal relationships between adjacent domains, we adapted the model so that relationships could exists between nonadjacent domains[19,127]. The premise was that understanding these relationships are important for glaucoma treatment and management.

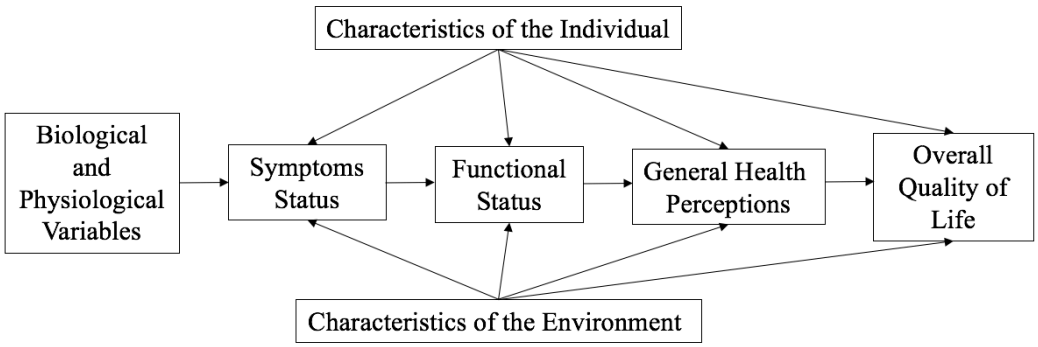


Figure 2-1. Health-related quality of life conceptual model. Developed by Wilson and Cleary, JAMA 1995; 273(1): 59-65

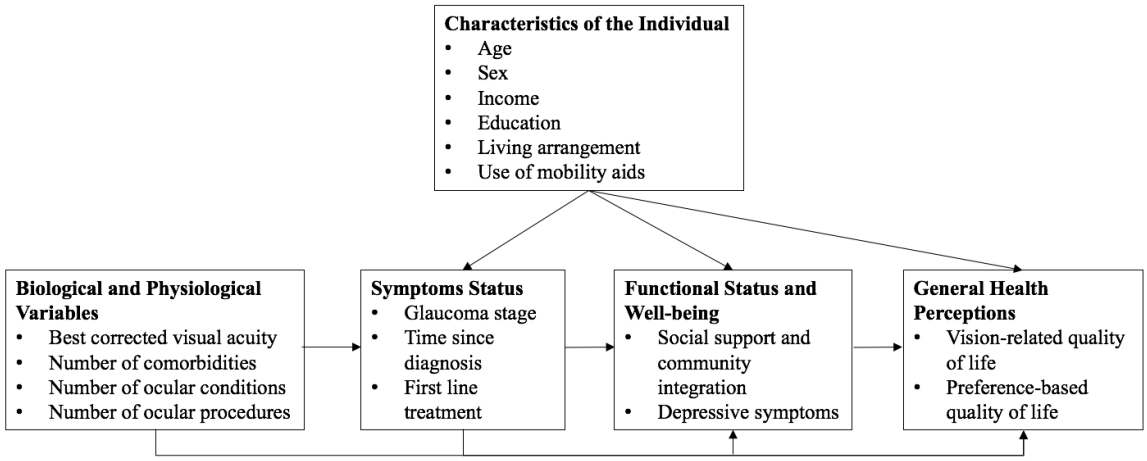


Figure 2-2. Adapted Wilson and Clearly (1995) model for glaucoma and glaucoma suspect patients

2.9 Predicting Patient-Reported Outcomes

The term *prediction* is used in machine learning to estimate the outcome for the value of a new unobserved variable[128]. In machine learning, no distinction is made between variables that could in principle be observed immediately (e.g. predict a patient's age, given their occupation) and those that are not observable until some future point in time (e.g. predict whether the patient will develop glaucoma over the next five years). Thus, the term *prediction* is relative to the state of knowledge of the model making the prediction, not relative to the "true" observed value of the variable. In machine learning, the variables in the model (i.e., input or independent variables) are

often called *predictor variables*[128]. For the context of this thesis, independent variables are referred to as *predictor variables.*

Predictive models may help ophthalmologists improve glaucoma management by assessing the patient's perceived health status and values. Such an approach is of high interest to governments which are interested in providing cost-effective, and yet, quality care. Compared to administering several different PRO instruments, a predictive tool can be an efficient method to assess patient needs for health care decisions. Studies aiming to predict outcomes or identify factors associated with an outcome need to go beyond simple regression models and significance of covariates to make conclusions. A literature review conducted in 2015 identified machine learning approaches used in clinical vision sciences for image processing and glaucoma diagnosis[23]. Most of the machine learning techniques in glaucoma research were used to improve the diagnosis of glaucoma[23].

Identifying predictor variables for HRQoL have been done in studies among conditions such as obesity, schizophrenia, multiple sclerosis, back pain, other chronic conditions and patients after undergoing surgical procedures[127,129–135]. However, the methodology used in identifying predictor variables is not consistent across studies. Benedict et al. (2005) and Kowalchuk et al. (2009) performed multivariable linear and/or logistic regression methods to identify the best subset of predictors of HRQoL and patient outcomes[130]. Bow-Thomas et al. (1999), Horng et al. (2005) and Khedmat et al. (2007) used stepwise regression to identify significant variables to be included in their predictive models[129,132,134]. Khedmat et al. (2007) further assessed the model accuracy of the derived model[134]. Hatzmann et al. (2009) and Heslin et al. (2011) used structural equation modeling to determine a final model to predict HRQoL[133,136]. Wang et al. (2013) identified factors associated with HRQoL among overweight/obese adults by using multivariable modeling and selected the best model based on Mallow's complexity parameter (Cp), R-squared, adjusted R-squared statistics[135].

There were a few studies that used machine learning techniques to predict PROs among patients with ocular conditions[95,137]. Browne et al. (2012) assessed model performance and model fit to estimate a model that predicts PROs (four generic HRQoL instruments and the NEI VFQ-25) based on vision-specific measures[95]. The model performance was assessed using mean absolute

error (MAE), mean square error (MSE) and root mean square error (RMSE), and model fit was assessed using R-squared [95]. The ordinary least squares model was chosen as the best-performing model, based on the lowest RMSE and MAE and highest R-squared [95]. The only clinical variables included in the model were visual acuity, contrast sensitivity and visual field[95]. Hirasawa et al. (2014) used the Sumi Visual Disability Questionnaire to predict VRQoL using only visual field and visual acuity, and the prediction error was calculated using RMSE with leave-one-out cross validation[137]. They found a smaller RMSE with the machine learning model compared to the linear and stepwise regression model[137].

Our research study is interested in performing machine learning techniques to identify variables that are most predictive of PROs. Not only were important clinical variables used, but important characteristics of patients that were not collected typically during a comprehensive eye exam were used as well.

2.10 Summary of the Gaps in the Literature

There is a growing recognition that it is important to assess patients' health outcomes in a multidimensional approach to include PROs, because there are many factors that influence health. Despite the benefits, it may be burdensome for ophthalmologists and patients to routinely assess PROs in clinical practice and there are no clinical guidelines specifying the use of PROs. Although, research studies have incorporated PROs, there is no specification as to which PRO is best to be used in ophthalmic practice. At a time when health policy makers are asking for metrics of quality of care, it is incumbent upon health care providers to develop and implement systems that efficiently address this need.

The importance of increasing patient input into health care decision making has become a very contemporary topic in many countries, including Canada. However, it has also been recognized that, this needs to be done in the most efficient way possible in order to be implemented and sustainable. Thus, our research study aims to identify predictor variables that are most strongly associated with PROs through rigorous methodologies that previous studies among glaucoma patients have not addressed.

Chapter 3

3 Thesis Rationale and Thesis Objectives

3.1 Thesis Rationale

There is an increased need to incorporate PROs in clinical care. In addition to the clinicians' assessment of the patient, PROs are necessary for tailored optimal care, because although patients have good clinical outcomes, their perceptions of their health state may be poor and vice versa. Obtaining data on PROs is also useful for policy makers to incorporate direct patient input into health care decision making policies. However, incorporating PROs to daily clinical practice can be challenge. A stream-lined process that would provide the highest yield of relevant data would allow for broad uptake in the clinical setting. Thus, my thesis aimed to answer the following question: What clinical and/or demographic variables are most predictive of important PROs? Pertaining to my project and patient population, important PROs are defined as social support and community integration, depressive symptoms, vision-related quality of life (VRQoL) and preference based health-related quality of life (HRQoL).

3.2 Thesis Objectives

1. To assess social support and community integration as measured by the Community Integration Questionnaire (CIQ), and determine which clinical and/or demographic variables are associated with the overall score, in glaucoma suspects and patients diagnosed with glaucoma.
2. To assess depressive symptoms as measured by the Patient Health Questionanire-9 (PHQ-9), and determine which clinical and/or demographic variables are associated with the presence or absence of depressive symptoms, in glaucoma suspects and patients diagnosed with glaucoma.
3. To assess VRQoL as measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), and determine which clinical and/or demographic variables are associated with the composite score, in glaucoma suspects and patients diagnosed with glaucoma.

4. To assess the preference-based HRQoL as measured by the Time Trade-Off (TTO) technique and determine which clinical and/or demographic variables are associated with the utility values, in glaucoma suspects and patients diagnosed with glaucoma.
5. To develop models for predicting social support and community integration, presence of depressive symptoms, VRQoL and preference-based HRQoL based on clinical and/or demographic variables, and validate the resulting models

Chapter 4

4 Methods

This chapter begins with an overview of the study design and sampling procedures (Section 4.1), sample size calculation (Section 4.2), and data collection methods (Section 4.3). Following is an overview of the predictor variables measured (Section 4.4) and outcome measures used (Section 4.5). This chapter concludes with a detailed description of the statistical analysis procedures (Section 4.6).

4.1 Study Design and Sampling Procedures

This study was a cross-sectional design. Two hundred and fifty patients who were identified as glaucoma suspects (refer to Section 4.4.2.5 for definition of glaucoma suspects) or had been diagnosed with glaucoma were recruited from a single ophthalmic practice with an ophthalmologist specializing in glaucoma, at the Ivey Eye Institute, St. Josephs Health Care London, Ontario. Patients were sequentially recruited from February to August 2016 using convenience sampling. As patients came in for their regular ophthalmology visits, their eligibility was determined by the ophthalmologist. Inclusion criteria included patients who were diagnosed with glaucoma or who were glaucoma suspects and their willingness and ability to answer the questions in the measurement tool. Exclusion criteria included patients who were unable to participate due to language restrictions. All participants received a complete explanation of the purpose and procedures involved in the study and patient concerns were addressed prior to study participation. Both verbal and written informed consent was obtained from all participating patients. The study was initiated after approval by Western University's Research Ethics Board (refer to Appendix A for the approval letter) and Lawson Health Research Institute's Clinical Research Impact Committee.

4.2 Sample Size Calculation

Since the Community Integration Questionnaire (CIQ) and Patient Health Questionnaire-9 (PHQ-9) measures were not previously assessed in our study population, the effect size for the sample size calculation was determined based on the Time Trade-Off (TTO) technique. The

effect size for the TTO utility score was determined based on the study conducted by Sharma et al. (2000)[138]. The power approach was used which involved specifying a hypothesis test, significance level (α), effect size and value of the power. For purposes of the sample size calculation, the null hypothesis is defined as the model with just the intercept (i.e., when all predictor variables = 0). The null hypothesis is testing whether the null model (i.e., model with only the intercept) is better than the alternative model with the predictor variables added. We determined the required Cohen's f^2 effect size for an F-test to be 0.2 and specified that such an effect be detected with 80% power, when the significance level is α=0.05 with 27 predictor variables (this includes the levels within a categorical variable). An online sample size calculator was used to calculate an a-priori sample size for multiple regression[139]. To compute the sample size, the online calculator used nine formulas that is provided in Appendix B[139].

The minimum required sample size calculated was n=139. Accounting for subject recruitment, we determined a study sample size of n=250 to be sufficient. In comparison, sample sizes of previous observational studies ranged from 73 to 325[87,95,96,119,124,125,138,140–153].

4.3 Data Collection Methods

Clinical and demographic variables were collected by two methods: face-to-face interviews and retrospective medical chart review. All data were recorded on paper data collection forms and then single data entry was performed into a password protected Microsoft Excel spreadsheet. Data quality checks were performed at random.

4.3.1 Face-to-face Interview

After the clinical examination, questionnaires were delivered in person. The actual administration of the questionnaires was a combination of interviewer administered and self-administration modes. Patients were interviewed under standardized conditions to determine five demographic variables and utility values by the Time Trade-Off (TTO) technique. The interviews were conducted by a single interviewer. All other questionnaires – Community Integration Questionnaire (CIQ) and Patient Health Questionnaire (PHQ-9) and the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) were completed by the patient in

paper format. The researcher was present while the patient was completing the questionnaires and was available to address any patient concerns and administer the questionnaire if patients had difficulties completing the questionnaires on their own.

4.3.2 Retrospective Chart Review

Clinical variables were obtained mainly through medical chart review or in combination with face-to-face interviews. A total of thirteen predictor variables were measured.

4.4 Predictor Variables

The Wilson-Cleary conceptual model[19] was adapted (Figure 2-2), review of the literature and expert opinions were used to refine and select variables to measure. Predictor variables were categorized to ensure adequate representation in each category.

4.4.1 Demographic Characteristics

Demographic characteristics collected include: age, sex, income, education, living arrangement and use of mobility aids. Typically, age and sex are variables that are collected and recorded in the patient's medical charts. However, income, education, living arrangement and use of mobility aids are variables that are not collected during a typical comprehensive eye exam.

4.4.1.1 Age

The Century Month Code (CMC) is a form of reporting dates that is used in major surveys such as the Demographic and Health Survey (DHS), to simplify working with data coded by month and year[154]. It represents dates using a reference date of January 1st 1900. CMC is calculated by multiplying the difference between the year of interest and 1900, by 12 and then adding the month:

$$\text{CMC (month, year)} = 12\ (\text{year} - 1900) + \text{month}$$

A continuous measure of age in years was calculated by computing the difference between the CMC of the date of visit and the date of birth.

4.4.1.2 Sex

Sex is a binary variable that was coded as Female = 1 (the reference category) and Male = 2.

4.4.1.3 Income

Current yearly income status of the patient was collected during the face-to-face interview. Patients were asked to choose their income range from the following eight categories: less than $10 000, $10 001 to 25 000, $25 001–$50 000, $50 001–$75 000, $75 001–$100 000, $100 001–$125 000, $125 001–$150 000 and greater than $150 000. To collect accurate income data these 8 categories were used. Prior to analysis, to obtain a better distribution of the data and exclude categories that do not contain any responses, the eight income categories were grouped into three categories: less than $25 000 (code = 1; the reference category), $25 000–$50 000 (code = 2) and greater than $50 000 (code = 3).

4.4.1.4 Education

Patients were asked to select their highest level of education completed from the following seven categories: some high school or less, completed high school, additional training (apprenticeship, trade or vocational school, etc.), college degree, undergraduate university, postgraduate university and advanced professional degree. For better data distribution, the response categories were collapsed to provide a binary variable: completed high school or less (code = 0; the reference category) and completed more than high school (code = 1).

4.4.1.5 Living Arrangement

Patients were asked to select their living arrangements given the following seven categories: home alone, home with spouse, home with family, home with caregiver, nursing home, long-term care home and retirement home. To exclude categories with no responses and for a better distribution of the data, the seven response categories were collapsed into three categories: home alone (code = 1; the reference category), home with family/spouse/caregiver (code = 2) and nursing/retirement home (code = 3).

4.4.1.6 Use of Mobility Aids

Patients were asked if they used mobility aids, and if they responded yes, then they were asked to specify the type of mobility aids used: a cane, walker, wheelchair or motorized scooter. This variable was dichotomized as: does not use mobility aid (code = 1; the reference category) and does uses mobility aid (code = 2).

4.4.2 Clinical Characteristics

The clinical characteristics collected include: best corrected visual acuity, number of comorbidities, number of ocular conditions, number of ocular procedures, glaucoma stage, time since diagnosis, initial treatment. These clinical characteristics are typically collected during a comprehensive eye exam.

4.4.2.1 Best Corrected Visual Acuity

Vision function is measured quantitatively through visual acuity and visual field assessments. Visual acuity measures the ability of the eye to identify shapes and details of objects at a given distance and to detect any changes in vision[70]. Best corrected visual acuity (BCVA) refers to the measurement 'with correction', such as with glasses or contact lens. Snellen acuity chart was used to test visual acuity for the study patients, in addition to Count Fingers (CF), Hand Motion (HM), Light Perception (LP) or No Light perception (NLP) for those patients whose vision was worse than 20/400.

The International Classification of Diseases (ICD-9) categorizes vision as: mild vision impairment (code = 1; the reference category), moderate vision impairment (code = 2) and legal blindness (code = 3). Mild vision impairment is defined as BCVA between 20/32 and 20/63; moderate vision impairment is defined as BCVA between 20/80 and 20/160; legal blindness is defined as BCVA is 20/200 or worse[71]. With regards to eye diseases that affect peripheral vision, as in glaucoma, it appears that the worse-seeing eye has a stronger influence on VRQoL[118]. Thus, the BCVA in the worse-seeing eye was obtained from the medical charts.

4.4.2.2 Number of comorbidities

First, patients were asked if they had any other comorbidities, and if yes, they were asked to specify the type of comorbidity by selecting from the following categories: cardiovascular, neurological, respiratory, immunocompromised, cancer, infectious disease, musculoskeletal, gastrointestinal, endocrine/metabolic, psychological and other.

Secondly, the researchers verified and validated the listed comorbidities by reviewing patients' medical charts. For analysis, the number of comorbidities was identified and treated as a continuous variable.

4.4.2.3 Number of Ocular Conditions

Patients were asked if they had any other ocular diseases besides glaucoma. All conditions such as cataracts, pseudoexfoliation syndrome, age-related macular degeneration were recorded. Patients' responses were verified through medical chart reviews. This variable was treated as a continuous variable.

4.4.2.4 Number of Ocular Procedures

Patients were asked if they had any ocular procedures performed, such as cataract surgery. Patients' response were verified through medical chart reviews. Number of ocular procedures was treated as a continuous variable.

4.4.2.5 Glaucoma Stage

The Canadian Ophthalmological Society defines four stages of glaucoma based on clinical characteristics[22]:

Suspect Glaucoma (code = 1; the reference category): suspicious cup-to-disc (C/D) asymmetry of >0.2.

Early Glaucoma (code = 2): Vertical C/D ratio of <0.65, and/or mild visual field defect not within 10 degrees of fixation, mean deviation(MD) better than -6dB.

Moderate Glaucoma (code = 3): Vertical C/D ratio between 0.7 and 0.85, and/or moderate visual field defect not within 10 degrees of fixation, MD from -6dB to -12dB.

Severe Glaucoma (code = 4): Vertical C/D ratio of >0.9, and/or visual field defect within 10 degrees of fixation, MD worse than -12dB.

Glaucoma stage was determined from the most recent clinical characteristics found in the patient's medical chart, and was treated as a categorical variable with four levels.

4.4.2.6 Time Since Diagnosis

Time since glaucoma or glaucoma suspect diagnosis was obtained from the patient's medical chart. The difference between the date of study visit and date of diagnosis was computed as a continuous measure. To improve the precision of this measure, the unit of measure was converted from years to months.

4.4.2.7 Initial Treatment

The treatment options for the study patients were obtained from medical charts, which included: medication (code = 0, the reference category), selective laser trabeculoplasty (SLT) (code = 1) or observation (code = 2). This variable was treated as a categorical variable with three levels.

4.5 Patient-Reported Outcome Measures

Four separate measurement tools were used to determine each of the four outcomes: patient's level of social support and community integration, presence of depressive symptoms, vision-related quality of life (VRQoL) and preference based HRQoL.

4.5.1 Community Integration Questionnaire

The CIQ was used to provide a quantitative indicator for the level of social support and ability to perform appropriate roles at home and within the community[108]. The CIQ contains 15-items and uses behavioural items of integration to achieve better reliability[60]. The CIQ used for this study is presented in Appendix B.

The CIQ was administered during the face-to-face interview process and took the patients about 5 to 10 minutes to complete. The CIQ was completed by the patient, with an interviewer present

for assistance. The original scoring procedures were followed for this study, which produced a total score and three subscale scores[107,108]:

> **Home Integration**: 0 to 10 points; consists of 5 items assessing activities that were typically done independently such as housework, child care, household shopping, meal preparation and planning social arrangements. The response options included: yourself alone, yourself and someone else or someone else.
>
> **Social Integration**: 0 to 12 points; consists of 6 items assessing frequency of activities that relate to leisure activities, shopping, personal finance management, visiting family and friends, having a best friend and engaging in leisure activities. The response options included the frequency of participating in such activities and with whom these activities are done with.
>
> **Productive Activities**: 0 to 7 points; consists of 4 items assessing frequency of activities that relate to volunteer activities, travel, student and employment status.

The total CIQ score ranges from 0 to 29, with a higher score representing a higher level of social support and complete community integration[108]. The CIQ was adapted for use in our research study. One of the options for item 10, '*Mostly with friends who have head injuries*' was changed to '*Mostly with friends*' to be applicable to our patient population. All other items remained the same. The total CIQ score was analyzed as a continuous outcome using linear regression.

Prior studies mainly assessed psychometric characteristics of the CIQ in a sample of traumatic brain injury patients, thus little is known about the psychometric properties among other patient groups[101]. However, a cross-sectional study published in 2010, tested the CIQ across various debilitating diseases, aging and traumatic conditions[74]. In addition, a recent study assessed the CIQ in a geriatric population[109]. Seale et al. (2002) reported relative reliability coefficients for home integration (r=0.71), social integration (r=0.70), productive activities (r=0.63) and CIQ total (r=0.81). In 2000, Cusick et al. reported intraclass correlation coefficients (ICC) as a measure of the test-retest reliability of the CIQ: 0.88 for home integration, 0.66 for social integration, 0.80 for productive activities and 0.86 for CIQ total[155]. Most recently, Singh &

Sharma (2015), reported excellent ICC among a geriatric population (ICC=0.99)[109]. Overall, studies have reported adequate to excellent test-retest reliability across the three domains.

Studies assessing the psychometric properties of the CIQ have reported evidence for discriminant validity comparing disabled to nondisabled individuals, differentiating scores among individuals living independently and with support and moderate to strong interrater reliability[101,106,108]. Past studies have reported the total CIQ score to be adequate in assessing community integration[105]. Reliability of the CIQ is generally acceptable and the validity was evaluated by difference in CIQ scores by sex, age and wheelchair use[106].

4.5.2 Patient Health Questionnaire - 9

The PHQ-9 was used to measure the presence of depressive symptoms. The PHQ-9 contains 9-items that represent *DSM-IV* specific diagnosis of depressive disorder[115]. The PHQ-9 used in our study is presented in Appendix C.

The PHQ-9 was completed by the patient, with an interviewer present for assistance. It took the patient about 5 minutes to complete the questionnaire. The PHQ-9 provides a total score that translates into the following four categories: minimal, mild, moderately severe and major depressive symptoms. Patients rate the difficulty of performing tasks such as: work, home activities and associations with others. Patients were asked how much each symptom has bothered them over the past two weeks, with respect to the following response options and scores: “not at all” (score = 0), “several days” (score = 1), “more than half the days” (score = 2) and “nearly every day” (score = 3). A final item assessed the degree to which the depressive symptoms influenced social, functional and occupational impairment[156]. The total PHQ-9 score was scored on a scale from 0 to 27, with the higher score representing more severe depressive symptoms. The scores assigned to the PHQ-9 categories are as follows: minimal symptoms (5 to 9), mild symptoms (10 to 14), moderately severe symptoms (15 to 19) and major depressive symptoms (> 20). The scoring scale used for PHQ-9 does not account for scores less than five. For our research study, to capture the PHQ-9 total scores of less than five, the score was dichotomized to the presence or absence of depressive symptoms. Thus, the score was categorized as ‘no depressive symptoms’ (code = 0; the reference category) and ‘some

depressive symptoms' (code = 1). 'No depressive symptoms' consisted of a PHQ-9 score ranging between zero and four and 'some depressive symptoms' consisted of a PHQ-9 score greater than four. The PHQ-9 score was analyzed as a binary outcome using logistic regression.

The PHQ-9 has strong internal and test-retest reliability as well as construct and factor-structure validity[156]. PHQ-9 demonstrated good internal reliability, with Cronbach's coefficient alpha values of 0.842, 0.846, 0.816 across three different trials[112]. Limited studies investigated the validity of PHQ-9. The sensitivity of the PHQ-9 detecting depressive disorders was fair (sensitivity=0.64)[114]. Kroenke et al. (2001) assessed the construct validity of the PHQ-9 using the Short Form General Health Survey and reported 88% sensitivity and specificity for a PHQ-9 score $\geq$10[115].

4.5.3 National Eye Institute Visual Function Questionnaire - 25

The NEI VFQ-25 was used to determine the vision-related quality of life (VRQoL) of the patients. It contains 25 items, 24 of which are vision-related. The NEI VFQ-25 used in our study is presented in Appendix D. The items were divided into three parts: general health and vision, difficulty with activities and responses to vision problems. The items were scored according to 12 domains: general health (1 item), general vision (1 item), ocular pain (2 items), near vision (3 items), distance vision (3 items), social functioning (2 items), mental health (4 items), role functioning (2 items), dependency (3 items), driving (3 items), colour vision (1 item) and peripheral vision (1 item)[157]. The driving score was only documented for patients who were drivers. Mean composite and subscale scores can be obtained from this questionnaire. Most items were recorded on a scale of 1 to 5 or 1 to 6, each item was then converted to a 0 (worst possible score) to 100 (best possible score) scale[18]. For purposes of this study, only the NEI VFQ-25 composite score was used to capture an overall measure of VRQoL. The NEI VFQ-25 composite score was an average of the 11 vision-related domains, with the exclusion of general health. The general health item was treated as a stand-alone item[157]. The composite score ranged from 0 to 100, with a higher score representing better visual functioning. By taking the average of each domain, as opposed to average of each item, equal weight was given to each domain[157]. NEI VFQ-25 was completed by the patient, with an interviewer present for assistance. Patients were asked to respond to all items as though they wore glasses or contact lenses to correct their

vision. It took the patient about 10 minutes to complete the questionnaire. The NEI VFQ-25 score was analyzed as a continuous outcome using linear regression.

Internal consistency estimates of each domain ranged from 0.71 to 0.85, representing an acceptable reliability[157]. Berdeaux et al. (2005) and Revicki et al. (2010), reported Cronbach's alpha coefficients for the NEI VFQ-25 composite score of 0.94 and 0.96, respectively[118]. Mangione et al. (1998) defined the psychometric properties of the NEI VFQ-25 and suggested that the 12 domains represent a broad dimension of VRQoL[100]. Mangione et al. (2001) tested the psychometric properties of the NEI VFQ-25 and reported evidence of between group validity[157]. The reliability and validity of NEI VFQ-25 was reported to be similar as the NEI VFQ-51[119]. On average the NEI VFQ-25 score predicts about 92% of the variance in the NEI VFQ-51 score[157]. Thus, previous studies demonstrated good reliability and validity of the NEI VFQ-25 in terms of measuring vision-related outcomes across various ocular diseases[158].

4.5.4 Time Trade-Off Technique

The TTO technique was used to obtain utility values. Patients were asked a 2-part question:

1. "*How many years do you expect to live?*"
2. "*Suppose that there was a new technology that could restore your eyesight to perfectly normal in both eyes. The technology always works but decreases the length of time you live. What is the maximum number of years, if any, that you would be willing to give up if you could receive this technology and have perfect vision for your remaining years?*"

The TTO utility values were calculated by dividing the number of years the patient is willing to give up for perfect vision by the number of years expected to live, and subtracting the obtained proportion from 1.0[148]. The utility value ranges between 0 (death) to 1 (perfect visual health). For example, consider a patient who expects to live for another 20 years and is willing to give up 5 years for perfect vision. The patient's utility value would be generated by subtracting the proportion of remaining years traded for perfect vision (0.25 or 25%) from the state of perfect visual health (1.0 or 100%). The resulting utility value of 0.75 (75%), represents the patient's perception of their HRQoL. The larger the proportion of remaining years that a patient is willing to trade for perfect vision, the lower the associated utility value. Generally, the TTO utility

values are analyzed using linear regression. However, given the data obtained for our study population, linear regression would not be the best fit, since it would result in a zero-inflated model. Therefore, for this study the utility values were categorized as those 'not willing to give up any years of life' (code = 0; the reference category) and those 'willing to give up some years of life' (code = 1). The format of the TTO technique used in our study is presented in Appendix E. The TTO technique was completed by the patient, with an interviewer present for assistance. The TTO utility score was analyzed as a binary outcome using logistic regression.

Previous studies have demonstrated the validity of the TTO technique with respect to best corrected visual acuity (BCVA) in the better-seeing eye[146]. TTO technique has shown good reproducibility[159]. Hollands et al. (2001) showed good reliability (ICC=0.76) of the TTO technique among patients with ocular disease[160].

4.6 Statistical Analysis

4.6.1 Univariate Analysis

Predictor variables were explored one by one, using univariate analysis. Descriptive statistics were computed for all predictor variables and outcome variables. In order to understand the distribution of each predictor variable, frequencies were calculated for categorical variables (sex, income, education, living arrangement, use of mobility aid, BCVA, glaucoma stage, initial treatment, PHQ-9 and TTO). In order to understand the central tendency and distribution of continuous predictor variables, means and standard deviations were calculated for continuous variables (age, number of comorbidities, ocular condition, ocular procedures, time since diagnosis, CIQ and NEI VFQ-25).

4.6.2 Missing Data

Missing data are classified in terms of their probability as they relate to the predictor variable (observed data) and outcome variables (unobserved data). Missing at random (MAR) is when the probability of missing data may depend on the predictor variables, but not on the outcome[161]. Missing completely at random (MCAR) is when the probability of missing data are not related to

the predictor variable and outcome variables[161]. Missing not at random (MNAR) is when the probability of missing data is related to the outcome variable[161]. MCAR and MAR can be imputed without introducing systematic bias[162].

Missing data can occur for many reasons. In our research study, it was due to patients' refusal to provide their income range and respond to the TTO technique. We believe the missing data were MAR conditioned on the other variables (i.e., education). The nonresponse rate was 7.2% (n=18) and 1.2% (n=3) for income and the TTO value, respectively. Considering that TTO value was an outcome of interest and the nonresponse rate was small, these individuals (n=3) were excluded from all analyses, reducing the sample size of 250 to 247.

Imputation is the method used to fill in missing data. The advantage of using imputation is to provide a complete data set for analyses, increase efficiency and reduce bias. Single imputation is a process that analyzes the observed responses for the missing variable and provides one plausible response for the missing data point. The advantage of single imputation is that once the values are filled in, performing the necessary complete-data analyses are straightforward[163]. The disadvantage of single imputation is that it underestimates the uncertainty and variance. To overcome this disadvantage, multiple imputation provides a set of plausible responses and considers the uncertainty both within and between imputations[161]. In multiple imputation, the missing values are replaced by two or more stimulated values to create imputed datasets[163]. Statistical analyses are then conducted using each of the imputed datasets to calculate a point estimate that is adjusted for the missing data uncertainty[163]. The objective of multiple imputation is to provide valid statistical inferences[163].

To handle the missing data for income in our dataset, an ordinal variable, multiple imputation was performed, using the ordered logistic regression imputation method in STATA 13. Literature suggest that values imputed between 2 and 10 are sufficient to obtain valid inferences and since the percentage of missing values is low for income, thus we imputed 10 times[163]. We then analyzed the multiple imputed data with multivariable linear and logistic regression. This method of multiple imputation was used to estimate regression coefficients, but not for stepwise regression and Classification and Regression Tree (CART) analyses.

It is more difficult to handle missing data in prediction modelling, because for nonlinear models like CART there are no standard rules for combining models from different imputations. This is in contrast to Rubin's Rules, which was used for the inference analyses[163]. Rubin's Rules are based on the approach of combining the models obtained from multiple imputation to produce overall estimates, confidence intervals and p-values. Since our predictive modelling is not intended for inference, it is less crucial to consider the uncertainty (e.g., standard errors of estimates), whereas for inference modelling uncertainty was important to consider. Furthermore, in our research study less than 10% of all measured variables were missing (entirely from the income variable). Thus, for prediction analyses, we performed single regression imputation using the mode, in which the mode of the 10 imputations was treated as the actual income value and manually replaced to create a complete data set. This approach increases variance, in comparison to the traditional mean substitution method. This completed data set was used to perform stepwise regression and CART analysis.

4.6.3 Bivariate Analysis

Bivariate analysis was performed to assess the unadjusted effect estimates and check whether each predictor variable and outcome were associated. Each of the 13 predictor variables were individually investigated for association with all four outcomes, using simple linear and logistic regression analyses.

4.6.4 Associations Between Predictor Variables

Investigating the association between the predictor variables can provide information regarding difficulties when assessing the effects (i.e., if two predictor variables present high correlation, then the effect of one, when adjusted for the other predictor variables, cannot be estimated with high precision)[164]. Comparisons can be made between categorical and categorical, or continuous and continuous, or categorical and continuous variables.

Pearson correlations were used to assess the association between pairs of continuous predictor variables. Correlation varies between -1 (perfect negative linear correlation) and +1 (perfect positive linear correlation), and 0 represents no correlation. The Pearson correlation coefficient threshold absolute value of 0.6 was used as a cut-off indicating a strong association between the

variables[165]. If a threshold above 0.6 was identified, then a significance test was conducted to confirm the association.

Chi-square tests were used to assess the association between pairs of categorical predictor variables. Chi-square test is based on the difference between the expected and observed frequencies. Probability ranges from 0 (categorical predictor variables are independent) to 1 (categorical predictor variables are dependent). The significance of the relationship between the predictor variables was defined at $\alpha<0.05$.

T-tests and one-way ANOVA were used to assess the associations between pairs of continuous and categorical predictor variables. T-test assess whether the means of two groups are statistically different from each other. ANOVA assess whether the means of three or more groups are statistically different from each other. Statistical significance was determined at $\alpha<0.05$. T-test was used for the categorical variables with two levels: sex, education and use of mobility aid. One-way ANOVA was used for the categorical variables with more than 2 levels: income, living arrangement, BCVA, glaucoma stage and initial treatment.

4.6.5 Regression Diagnostics

The following assumptions were considered to examine the distribution of the predictor variables: linearity, normality, homoscedasticity, multicollinearity, model specification, independence. The linearity assumption considers that the relationship between the predictor variables and the outcomes should be linear. Component-plus-residual plot was used to assess for non-linearity. The normality assumption requires that the residuals are normally distributed, which was assessed using quantile-quantile (Q-Q) plot. The homoscedasticity assumption requires that the error variance be constant, which was assessed using residual-versus-fitted plot. Lastly, the variance inflation factor (VIF) was used to test for multicollinearity. A VIF of 10 was used as the rule of thumb to indicate an acceptable level of multicollinearity[166].

4.6.6 Multivariable Regression Analysis

Inferential statistical analysis was performed to generalize about the population from which the sample was taken[167]. Valid inference means that the standard errors of the parameter estimate are

valid, confidence intervals have the desired coverage probability and p-values correctly describe the probability of observing the absolute value of the observed parameter estimate[168].

Multivariable linear and logistic regression analyses were performed using STATA 13.

4.6.6.1 Multivariable Linear Regression

A multivariable linear regression model was built to identify the predictor variables associated with the following two outcomes: social support and community integration; and VRQoL. Multivariable linear regression models the relationship between a set of predictor variables on the likelihood of one continuous outcome, by fitting a linear equation to the observed data.

The equation for systematic part of the model is:

$$E(y|x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

where $E(y|x)$ is the expected value of the outcome at a given value of a set of predictor variables

x_i (i = 1, 2, … n) are the predictor variables

β_0 is the intercept

β_i (i = 1, 2, … n) are the slopes for each variable (i.e., regression coefficients)

The intercept, (β_0), denotes the probability of the outcome when x_i = 0, which can be interpretable by "centering" the continuous predictor variables. For the continuous predictor variables, the coefficient, β_i ,is interpreted as the change in the expected outcome for a one unit increase in one predictor variable, while holding all other predictor variables in the model constant. For categorical predictor variables, we get the probability of the outcome in the group with respect to the reference group, adjusting for all other predictor variables.

There is also a random part of the model, in which each observation of the outcome is modeled in terms of an error term[168].

The equation for the random part of the model is:

$$y_i = E(y_i|x_i) + \varepsilon_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_n x_{ni} + \varepsilon_i$$

where ε_i is the error term about an average determined by x_i

x_{ji} (i = 1, 2, … n) is the value of the predictor variable x_j for observation i

We assume that ε_i is normally distributed with a mean of zero.

Linear regression diagnostics were checked to ensure the data met the assumptions of linear regression and to avoid potential bias of the parameter estimates. Normality of residuals was assessed using residual plots. Homogeneity of variance of the residuals (homoscedasticity) was assessed using a residual-versus-fitted plot. Multicollinearity was assessed using variance inflation factor (VIF). Linearity was assessed for each continuous predictor variable using component-plus-residual plots. Specification error was tested using a link test.

4.6.6.2 Multivariable Logistic Regression

A logistic regression model was built to identify the predictor variables associated with the following two outcomes: presence of depressive symptoms and preference based HRQoL. Logistic regression models the effect of a set of predictor variables on the likelihood of one binary outcome.

The equation for multivariable logistic regression is:

$$logit(\pi_i) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

where π_i is the probability of the outcome

X_i (i = 1, 2, … n) are the predictor variables

β_0 is the intercept

β_i (i = 1, 2, … n) are the regression parameters

$logit$ is the ln (odds of the outcome), where odds is $(\frac{\pi_i}{1-\pi_i})$

The intercept (β_0) denotes the log of the odds of the outcome when all $X_i = 0$, which may or may not contain meaningful interpretation, but is still an integral part of the model. We obtain the odds of the outcome when $X_i = 0$ by exponentiating the intercept. By exponentiating the regression coefficient (β_i), we get the odds ratio of the outcome. For the continuous predictor variables, exponentiating the coefficient will provide the odds ratio of the outcome for every one unit increase in X_i, adjusting for all other predictor variables. For categorical predictor variables, we get the odds ratio of the outcome comparing the higher category of X_i to its reference category, adjusting for all other predictor variables.

Logistic regression diagnostics were checked to ensure linear relationship with the logit of the outcome and absence of multicollinearity. Linearity between the continuous predictor variables and the logit of the outcome was assessed using scatter plots. Multicollinearity was previously assessed using VIF.

4.6.7 Variable Selection for Building Prediction Models

The primary aim of prediction is to minimize error rather than identifying associations[168]. Variable selection for prediction purposes is intended to select the best set of predictor variables. In terms of prediction, variable selection is valuable so that we can save time and money by not measuring redundant predictor variables. The aim is to construct a model that predicts the value of the outcome given the predictor variable. Stepwise regression and Classification and Regression Tree (CART) are machine learning approaches to variable selection.

Some predictor variables are well-established in literature as being highly associated with the outcome, thus predictor variables may be included in the model for face validity without considering the strength or statistical significance[168]. Selecting predictor variables based on p-values have been criticized, since no significance of an effect is not equal to the absence of an effect[168]. Variable selection is important as it aims to determine which variables are strong predictor variables of the outcome and to find the right balance between goodness of fit and parsimonious model. Variable selection can improve interpretability and accuracy of the predictions. A parsimonious model is one that achieves a desired level of prediction with as few predictor variables as possible.

With building the "best" predictive model, the issue lies in having to choose predictor variables from a larger set[169]. It is not just sufficient to perform automatic statistical variable selection, but it is important to consider clinical significance as well.

4.6.7.1 Stepwise Regression

There are several different methods used to select predictor variables when fitting a regression model. Forward selection starts with no predictor variables in the model and then tests the addition of each predictor variable. Backward elimination starts with all predictor variables in the model and then tests the removal of each predicator variable. Stepwise regression is combination of forward selection and backward elimination. It is an automated approach used in exploratory model building to select predictor variables. During this method, predictor variables are systematically added and/or removed, beginning with a model that has all the variables in it. The predictor variables that are dropped during stepwise regression may still be correlated with the outcome, but provide no additional explanatory effect beyond the predictor variables already included in the model[168]. The number of possible models is dependent on the number of predictor variables[170]. For example, five predictor variables yield $2^5 = 35$ possible regression models. These models are fit based on a criterion, from which the best model is chosen. Automatic methods are useful when there are many predictor variables and it is not feasible to fit all possible models.

Information criteria is a measure of goodness of fit that takes into account both predictive accuracy and model complexity. Under-fitting a model may not capture the true variability of the outcome, and over-fitting a model can lose generalizability. Akaike Information Criterion (AIC) was introduced as a tool for optimal model selection:

$$AIC = -2\ell + 2p$$

where ℓ is the maximized log-likelihood

p is the number of parameters included in the model

AIC considers both the model fit and number of predictor variables used, it is not a p-value driven approach. The AIC value is measured as the likelihood of the parameters estimates being correct for the population based on the observed data. Stepwise regression with AIC

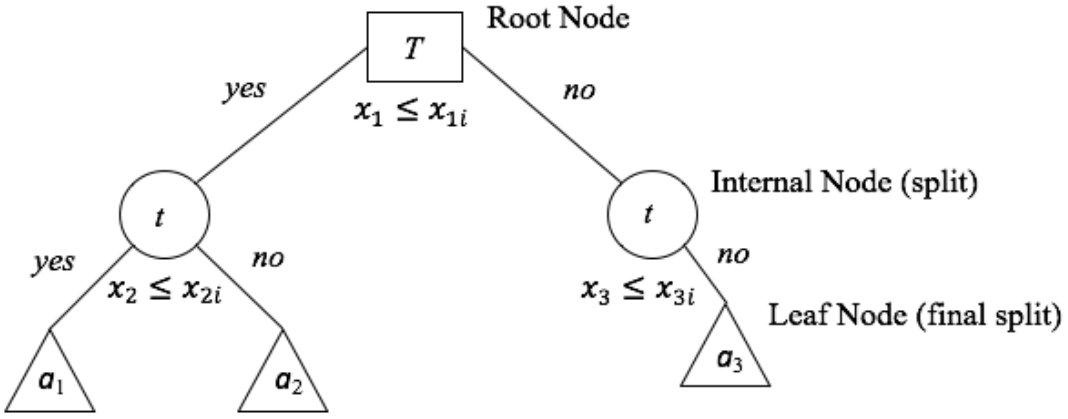
simultaneously evaluates a subset of possible multiple regression models to find the best model[171]. AIC measures the balance between the amount of explanatory power and the model size. The model with the smallest AIC value is determined as the better model.

We performed stepwise model selection by AIC using R (package 'MASS')[172].

4.6.7.2 Classification and Regression Trees

CART analysis is a machine learning method used to create a decision tree that predicts the outcome based on several predictor variables and helps to determine the "most" important predictor variables of the outcome. It is a visual representation of the relationship among the important predictor variables and the outcome. Classification tress are for binary outcomes and regression trees are for continuous outcomes[173]. The goal is to use a training sample of observations and find a model to predict values of the outcome from new values of the predictor variables[173]. CART also captures interaction effects between predictor variables.

The basic structure and splitting algorithm of CART is shown in Figure 4-1:



$$E(y|x_1, x_2, x_3) = \begin{cases} a_1 \; if \; x_1 \leq x_{1i} \; and \; x_2 \leq x_{2i} \\ a_2 \; if \; x_1 \leq x_{1i} \; and \; x_2 > x_{2i} \\ a_3 \; if \; x_1 > x_{1i} \; and \; x_3 > x_{3i} \end{cases}$$

Figure 4-1. The basic structure and splitting algorithm of Classification and Regression Trees

Each node is conditioned on a predictor variable, x_i , starting at the root node. The final split is called the leaf node and the terminal node, a_x , indicates that further splitting of the data does not have enough variance to explain the outcome. CART is built using a splitting algorithm that splits the data into smaller parts based on yes/no questions with maximum homogeneity[174]. Maximum homogeneity is defined by an impurity function ($i(t)$).

Gini Index is the impurity function commonly used for classification trees. The Gini Index defines the node splits, where each split maximizes the decrease in impurity[173]:

$$i(t) = 1 - \sum_{k=1}^{K} p^2(k|t)$$

where k is the index of the class

$p(k|t)$ is the conditional probability of class k in node t

Regression trees do not have classes, instead response vectors of the outcome are used. Like the Gini index, for regression trees the splitting is made according to the squared residuals minimization algorithm[173]:

$$min_{x_i \leq x_i^R}[P_l Var(Y_l) + P_r Var(Y_r)]$$

where $Var(Y_l), Var(Y_r)$ is the response vector for the left and right internal nodes

$x_i \leq x_i^R$ ($i = 1, 2 \ldots n$) is the optimal splitting rule

A larger initial tree was created with recursive partitioning, where a split was determined by examining all possible split values for each variable to find the best split. Then the tree was pruned with a cross-validation method, to create an optimal tree and minimize misclassification error. To validate the tree a cost-complexity parameter (C_P) is used. The least C_P value indicates that the cross-validated error of the tree is minimum to determine true predictive power of the tree. The C_P function is[175]:

$$R_\alpha(T) = R(T) + \alpha|\widetilde{T}|$$

where T is the number of terminal nodes or complexity of the tree

$R(T)$ is the resubstitution misclassification error of the tree T

$|\widetilde{T}|$ is the number of terminal (or "leaf") nodes in the tree

$\alpha|\widetilde{T}|$ is the complexity measure that depends on $\tilde{T}$ for a given value α

CART analysis was performed using the 'rpart' package implemented in R (package 'rpart'). By default, 'rpart' conducts as many splits as possible, then uses 10-fold cross-validation to prune the tree.

4.6.8 Model Assessment

Model assessment is based on the models ability to accurately predict new data (i.e., prediction) and whether the model accurately describes the associations in the current data (i.e., goodness of fit)[168].

To avoid results by chance, the data can be split several different times to create two data sets – training and validation[176]. The validation set is used to estimate the error rate of the training set. Assessing the average performance of a model over the different splits is referred to as cross-validation. Cross-validation is a model validation technique for assessing how the results will be generalizable. It is mainly used to estimate how accurately a model will perform and compare the performance of different models.

Since the data set had 250 observations, we chose to perform leave-one-out cross validation (LOOCV), where a single observation is used for the validation set and n-1 is used for the training set[177]. This procedure is repeated so that each observation in the original data set has been a part of the validation set. LOOCV evaluates a model based on prediction and is used for estimating the test error[176]. In comparison to k-fold cross validation, the LOOCV approach has less bias and does not overestimate the test error rate, since the training sets used contain n-1 observations[177]. The LOOCV estimate for the mean squared error (MSE) is the average of n test error estimates[177]:

$$LOOCV_n = \frac{1}{n}\sum_{i=1}^{n} MSE_i$$

where MSE_i is represented by $(y_i - \hat{y}_i)^2$ and $\hat{y}_i$ is the prediction made for the excluded observation.

The absolute error (AE) is the difference between the measured and actual values. The mean absolute error (MAE), standard error (SE) and standard deviations (SD) were used to summarize the errors and describe the predictive performance of each model. MAE is a good indicator of average model performance and is widely used in model evaluation[178]. The MAE is calculated as:

$$MAE = \frac{1}{n}\sum_{i=1}^{n} |e_i|$$

where e_i $(i = 1, 2, \ldots, n)$ is the *n* samples of model errors produced by LOOCV

n is the sample size

SE quantifies the variability of estimated parameters for precision, whereas SD measures the variability of the data from the mean[179]. SD of the AE is defined as:

$$SD_{AE} = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(|e_i|^2 - MAE)^2}$$

The underlying assumption with SE is that the errors are unbiased and follow a normal distribution, which provides a representation of the error distribution. SE of the estimate of MAE is calculated as:

$$SE_{MAE} = \frac{SD_{AE}}{\sqrt{n}}$$

4.6.9 Software

All preliminary and main analysis were executed using STATA 13 and R (version 1.0.136)

Chapter 5

5 Results

This chapter first presents the characteristics of the study population and the results of imputation (Section 5.1 and 5.2). Following is a discussion of the associations among the predictor variables (Section 5.3) and a statement of the regression diagnostics performed (Section 5.4).
Section 5.5 provides an overview of all the analyses conducted –bivariate analysis, multivariable regression analysis, stepwise regression, Classification and Regression Trees (CART), and model assessment. Section 5.6 presents the results for each of the four PROs – social support and community integration, presence of depressive symptoms, vision-related quality of life (VRQoL) and preference-based HRQoL.

5.1 Characteristics of the Study Population

Univariate analysis was performed to determine the characteristics of the study population. A total of 250 patients consented to participate in the study. The patients' demographic characteristics are presented in Table 5-1. The average age of the study population [mean (SD)] was about 72.9 (10.2) years. The sex distribution was 60% female. The majority of patients were Caucasian (80%) and lived at home with their family, spouse or caregiver (69%). About half had completed high school or less (49%) and about 40% had an income of less than $25,000. Only about 11% used a mobility aid such as a cane, walker, wheelchair or motorized scooter.

The patient's clinical characteristics are presented in Table 5-2. The majority of patients had mild vision loss (72%) based on the best corrected visual acuity (BCVA) in the worse-seeing eye and received medication as their initial treatment (72%). About 33% of the patients were diagnosed as glaucoma suspects and only about 15% were diagnosed with severe glaucoma. The average number of comorbidities in the study population [mean (SD)] was 1.6 (1.5), average number of ocular conditions was 2.1 (1.1), average number of ocular procedures was 1.1 (1.0) and average time since diagnosis was 100.7 (74.5) months.

5.2 Missing Data

Imputation of the missing values for the income variable was performed and the distribution of the pre-imputed values did not greatly differ from the distribution of the post-imputed values (Table 5-3).

5.3 Associations Among Predictor Variables

5.3.1 Association Between Pairs of Continuous Predictor Variables

The results of the associations between continuous predictor variables are presented in Table 5-4. Pearson correlations did not reveal any strong linear associations among the continuous predictor variables: age, number of comorbidities, number of ocular condition, number of ocular procedures and time since diagnosis.

5.3.2 Associations Between Pairs of Categorical Predictor Variables

The chi-square test results of the associations between categorical predictor variables are presented in Table 5-5. Significant associations were observed between sex and income. A greater number of females (46%) had an income of less than $25 000. Sex was also significantly associated with living arrangement. A greater number of males (77%) were living at home with others. A significant association was observed between education and use of mobility aid. About half of the patients who did not use mobility aids, had completed more than high school (54%). BCVA was found to be significantly associated with the use of mobility aid and glaucoma stage. Among the patients who did not use mobility aids, significantly more patients had mild visual acuity loss (92%), compared to only 9% who had severe glaucoma.

5.3.3 Associations Between Pairs of Continuous and Categorical Predictor Variables

The t-test and one-way ANOVA results for the associations between continuous and categorical predictor variables are presented in Table 5-6. Age was significantly associated with income, living arrangement, use of mobility aid, BCVA and glaucoma stage. On average, patients with an income of less than $25 000, living in a nursing or retirement home, using a mobility aid, moderate visual acuity loss and severe glaucoma were slightly older. Number of comorbidities

was significantly associated with sex. Number of ocular conditions was significantly associated with BCVA. Number of ocular procedures was significantly associated glaucoma stage and initial treatment. Time since diagnosis was significantly associated with initial treatment. On average, patients who had medication as their initial treatment, had a higher number of ocular procedures and greater time since diagnosis.

5.4 Regression Diagnostics

The component-plus-residual plots, Q-Q plots, residual-versus-fitted plots and the variance inflation factors confirmed the assumption of linearity, normality, homoscedasticity and multicollinearity, respectively.

5.5 Overview of the Statistical Analyses

5.5.1 Bivariate Analysis for Unadjusted Effects

The bivariate analysis results for social support and community integration; presence of depressive symptoms, VRQoL and preference-based HRQoL with the demographic and clinical predictor variables are presented in Tables 5-7 and 5-8; 5-13 and 5-14; 5-19 and 5-20; 5-25 and 5-26, respectively. There was a total of 13 predictor variables included, of which six were demographic and seven were clinical variables. A significance level of $p \leq 0.05$ was used to determine variables that were significantly associated with the PRO.

5.5.2 Multivariable Regression Analysis for Adjusted Effects

Multivariable regression analysis results for social support and community integration; presence of depressive symptoms, VRQoL and preference-based HRQoL are presented in Tables 5-9, 5-15, 5-21 and 5-27, respectively. All predictor variables identified through review of the literature, expert opinion and conceptual model were included in the multivariable analyses. A significance level of $p \leq 0.05$ was used to determine variables that were significantly associated with the outcome.

5.5.3 Variable Selection for Developing Prediction Models

5.5.3.1 Stepwise Regression

Stepwise regression by Akaike Information Criterion (AIC) for social support and community integration; presence of depressive symptoms, VRQoL and preference-based HRQoL are presented in Tables 5-10, 5-16, 5-22 and 5-28, respectively. The selected model was based on the lowest AIC value.

5.5.3.2 Classification and Regression Trees

Classification and Regression Tree (CART) is an effective machine learning technique, commonly used for developing prediction models[180]. Classification trees are used for categorical outcomes and regression trees are used for continuous outcomes. Recall that CART qualitatively expresses the relationship between the predictor variables and each outcome by repeatedly splitting the data based on one predictor variable. At each split the data is divided into two groups[174]. The objective is to create a reasonably small tree to avoid overfitting the data and identify the relevant predictor variables. To avoid overfitting, after the splitting procedure creates the initial tree with the maximum number of splits, the tree is pruned to obtain the optimal tree with the most important variables. When a pruned tree results in zero splits, this suggests that there isn't enough signal within the data to justify a tree model.

5.5.4 Model Assessment for Developing Prediction Models

The leave-one-out cross validation (LOOCV) method was used to assess the predictive performance of each outcome. The mean absolute error (MAE), standard error (SE) and standard deviation (SD) for the models built for social support and community integration; presence of depressive symptoms; VRQoL and preference-based HRQoL are presented in Tables 5-12, 5-18, 5-24 and 5-30, respectively. In addition to the four variable selection methods (selected multivariable regression, stepwise regression, initial CART and pruned CART), the initial multivariable regression model and the baseline model were assessed for comparison. The baseline model, with only the intercept, is the worst possible model. First, the model with the lowest MAE was selected, and all plausible models were selected if it was within one SE from the lowest MAE. Of all plausible models, the most promising model was determined based on

the model with the lowest number of variables selected. This procedure for selecting the most promising model was followed by the methodology outlined by Hastie et al. (2008)[128].

5.6 Results for Each Patient-Reported Outcome

5.6.1 Social Support and Community Integration

Recall, that the Community Integration Questionnaire (CIQ) score was used to measure social support and community integration on a scale from 0 to 29, in which a higher score represents complete community integration and a higher level of social support. In our study population, the average CIQ total score was 17.9±5.0, with a minimum average score of two and maximum of 28. Thus, majority of the patients had moderate social support and community integration.

5.6.1.1 Unadjusted Effects of Social Support and Community Integration

The bivariate analysis for social support and community integration with the demographic variables is presented in Table 5-7, and for clinical variables it is presented in Table 5-8. The following five demographic variables were significantly associated with social support and community integration: age ($p < 0.0001$), sex ($p < 0.0001$), income ($p < 0.0001$), living arrangement ($p<0.0001$), and use of mobility aid ($p < 0.0001$). On average, for every year increase in age, the expected social support and community integration decreases by 0.17±0.03 (95% CI = -0.22 to -0.11). On average, males are expected to obtain a lower social support and community integration than females (-3.18±0.61, 95% CI = -4.39 to -1.97). Patients with an income between $25 000 to $50 000 (2.17±0.76, 95% CI = 0.66 to 3.67) and greater than $50 000 (2.95±0.77, 95% CI = 1.44 to 4.47), on average, are expected to obtain social support and community integration that is greater than patients with income less than $25 000. On average, patients living at home with others (-1.97±0.67, 95% CI = -3.30 to -0.65) and living in a nursing/retirement home (-9.26±2.48, 95% CI = -14.15 to -4.38), are expected to obtain social support and community integration that is lower than patients living at home alone. Patients using a mobility aid, on average, are expected to obtain social support and community integration that is lower than patients who do not use a mobility aid (-4.96±0.95, 95% CI = -6.84 to -3.09).

The only clinical variable that was found to be significantly associated with social support and community integration was moderate visual acuity loss ($p = 0.01$). On average, patients with moderate visual acuity loss are expected to obtain social support and community integration that is lower than patients with mild visual acuity loss (-2.23±0.89, 95% CI = -3.98 to -0.47).

5.6.1.2 Adjusted Effects Social Support and Community Integration

The estimated coefficients and p-values from the multivariable linear regression analysis with social support and community integration as the dependent variable are presented in Table 5-9. The five variables that were found to be significant with social support and community integration are: age ($p < 0.0001$), sex ($p < 0.0001$), income ($p < 0.0001$), living arrangement ($p < 0.0001$) and use of mobility aid ($p = 0.003$). Adjusting for all predictor variables, for every year increase in age, on average the expected social support and community integration decreases by 0.15±0.03 (95% CI= -0.21 to -0.09). On average, males are expected to obtain a lower social support and community integration than females (-3.28±0.56, 95% CI= -4.38 to -2.18). Patients with an income greater than $50 000, on average, are expected to obtain social support and community integration that is greater than patients with income less than $25 000 (3.07±0.66, 95% CI= 1.77 to 4.37). Patients living at home with others (-2.58±0.59, 95% CI=-3.75 to -1.41) and in nursing home or retirement home (-7.92±2.12, 95% CI= -12.09 to -3.74), on average, are expected to obtain social support and community integration that is lower than patients who are living at home alone. Patients using a mobility aid, on average, are expected to obtain social support and community integration that is lower than patients who do not use a mobility aid (-2.63±0.87, 95% CI= -4.34 to -0.92).

No clinical variables were found to be significantly associated with the CIQ score. When controlling for all variables, age, sex, living arrangement and use of mobility aid had a negative relationship with social support and community integration, and income had a positive relationship. The overall model was significant ($p < 0.0001$), with a generalized R-squared of 0.42, suggesting that 42% of the variance in CIQ score is explained by this multivariable regression model.

5.6.1.3 Stepwise Regression for Social Support and Community Integration

The results from stepwise regression analysis by AIC for social support and community integration is presented in Table 5-10. The initial model for social support and community integration consisted of the 13 predictor variables and had an AIC value of 706.19. The final model with the lowest AIC value of 690.61, consisted of the following five predictor variables: age, sex, income, living arrangement and use of mobility aid.

5.6.1.4 Regression Tree for Social Support and Community Integration

The initial regression tree of social support and community integration is presented in Figure 5-1, where the data were split (root node) using the variable 'use of mobility aid' and the final split (leaf node) contained the predicted score obtained from the CIQ, ranging from 0 to 29. For example, a patient who does not use mobility aid, is a male and is not ≥ 62 years of age, has a predicted score of 21 (range = 0 to 29). The initial regression tree has 12 nodes, whereas the pruned tree in Figure 5-2 has only three nodes.

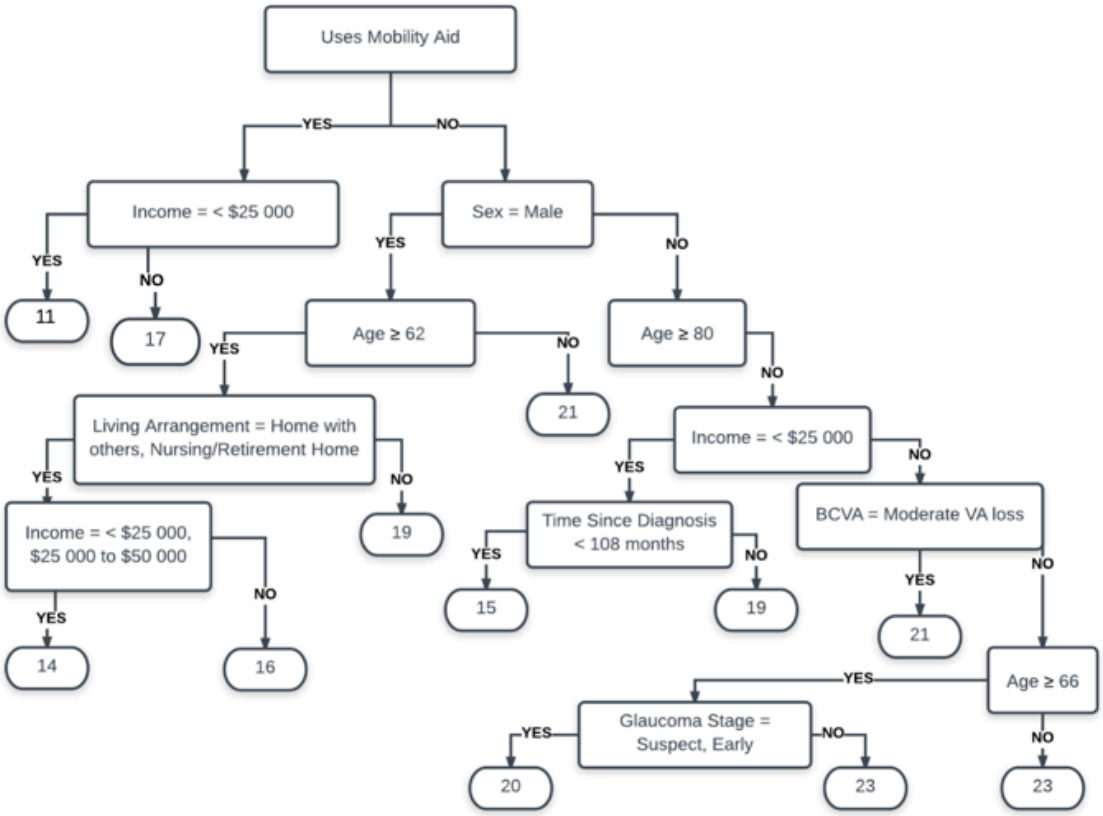


Figure 5-1. Initial regression tree for social support and community integration

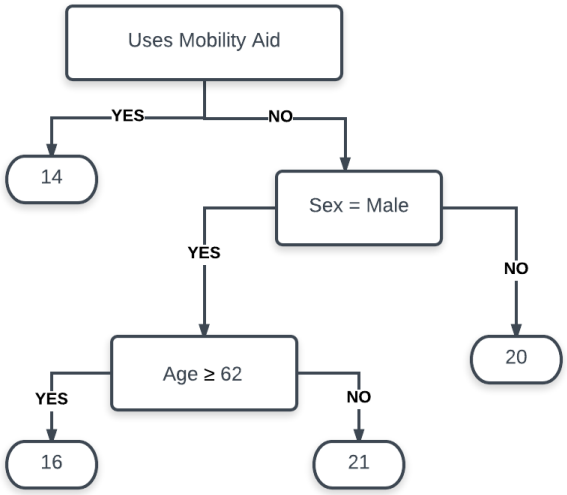


Figure 5-2. Pruned regression tree for social support and community integration

5.6.1.5 Variable Selection for Social Support and Community Integration

The selected variables from multivariable regression, stepwise regression by AIC, initial and pruned CART analyses for predicting social support and community integration are presented in Table 5-11. Eight variables were selected from the initial CART analysis, five variables were selected from multivariable and stepwise regression by AIC and three variables were selected from the pruned CART analysis. Age, sex and use of mobility aid were selected from all four methods. Income and living arrangement were selected from two of the four methods. Education, number of comorbidities, number of ocular conditions and number of ocular procedures were not selected from any of the methods. Thus, the main predictor variables explaining patients social support and community integration among our patient populations seems to be age, sex and use of mobility aids.

5.6.1.6 Model Assessments for Social Support and Community Integration

The model with the lowest MAE for the social support and community integration outcome is stepwise regression model by AIC, with a MAE of 3.21. The plausible models are the models with a MAE of 3.37 or less, which include: initial multivariable regression model and selected multivariable regression model. From Table 5-12, of the plausible models, the model with the

lowest number of predictor variables is the selected multivariable and stepwise regression model. Therefore, the most promising predictor variables of social support and community integration are presented in the model below:

$$\textbf{\textit{Social support and community integration}} = \alpha + \beta_1 (age) + \beta_2 (sex) + \beta_3 (income) + \beta_4 (living\ arrangement) + \beta_5 (use\ of\ mobility\ aid)$$

5.6.2 Presence of Depressive Symptoms

Recall, that the Patient Health Quesionnaire-9 (PHQ-9) total score was dichotomized as 'no depressive symptoms' and 'some depressive symptoms' (refer to Section 4.5.2). Among the study population, about 79% reported having no depressive symptoms. In other words, on the original PHQ-9 scale (score range: 0 to 27), 79% of the patients reported a score of four or less.

5.6.2.1 Unadjusted Effects of the Presence of Depressive Symptoms

The bivariate analysis for the presence of depressive symptoms with the demographic variables is presented in Table 5-13, and for clinical variables it is presented in Table 5-14. The following four demographic variables were significantly associated with the presence of depressive symptoms: income ($p = 0.04$), education ($p < 0.0001$), living arrangement ($p = 0.04$), and use of mobility aid ($p < 0.0001$). Patients with an income greater than $50 000 (OR = 0.43, 95% CI = 0.19 to 0.96), on average, were less likely to report having depressive symptoms than patients with income less than $25 000. On average, patients who completed more than high school were less likely to report having depressive symptoms than patients who completed high school or less (OR = 0.50, 95% CI = 0.27 to 0.93). Patients who used mobility aid, on average, were more likely to report having depressive symptoms than patients who did not use mobility aid (OR = 3.31, 95% CI = 1.46 to 7.53).

Initial treatment ($p < 0.0001$) was the only clinical variable that showed significant association with the presence of depressive symptoms.

5.6.2.2 Adjusted Effects of the Presence of Depressive Symptoms

The estimated odds ratio and p-values from the multivariable logistic regression analysis with the presence of depressive symptoms as the dependent variable, are presented in Table 5-15. Two

variables were significantly associated with the presence of depressive symptoms: use of mobility aid (p = 0.006) and initial treatment (p = 0.01). Patients who used a mobility aid were more likely to report having depressive symptoms than patients who did not use a mobility aid (OR=4.37, 95% CI=1.59 to 12.05). Patients who had selective laser trabeculoplasty as their initial treatment (OR=3.52, 95% CI=1.42 to 8.75) and no initial treatment (OR=3.24, 95% CI=1.02 to 10.27) were more likely to report having depressive symptoms than patients who had medication as their initial treatment.

The generalized R-squared is not interpreted the same way for logistic regression, as it is in linear regression. Rather, the pseudo R-squared measure is used in logistic regression and it is defined as the following:

$$1 - \frac{\log likelihood\ of\ the\ full\ model, with\ the\ intercept}{\log likelihood\ of\ the\ model\ with\ only\ the\ intercept}$$

The pseudo R-squared corresponds to a proportional reduction in the error variance[181]. The overall model for the presence of depressive symptoms was significant (p = 0.04), with a pseudo R-squared of 0.16.

5.6.2.3 Stepwise Regression for the Presence of Depressive Symptoms

The stepwise regression analysis by AIC for the presence of depressive symptoms is presented in Table 5-16. The initial model for presence of depressive symptoms consisted of the 13 predictor variables and had an AIC value of 258.39. The final model with the lowest AIC value of 247.71, consisted of the following seven predictor variables: age, sex, education, living arrangement, use of mobility aid, number of comorbidities and initial treatment.

5.6.2.4 Classification Tree for Presence of Depressive Symptoms

The initial classification tree for presence of depressive symptoms is presented in Figure 5-3, where the data were split (root node) using the variable 'use of mobility aid' and the final split (leaf node) contained the predicted probability of having depressive symptoms (0 = no depressive symptoms). For example, a patient who does not use mobility aids, who's initial treatment is medication, is ≥ 62 years of age and time since diagnosis is < 138 months, was

predicted to have a 0.077 probability of having depressive symptoms. The initial classification tree has 12 nodes, and pruning the tree resulted in zero splits.

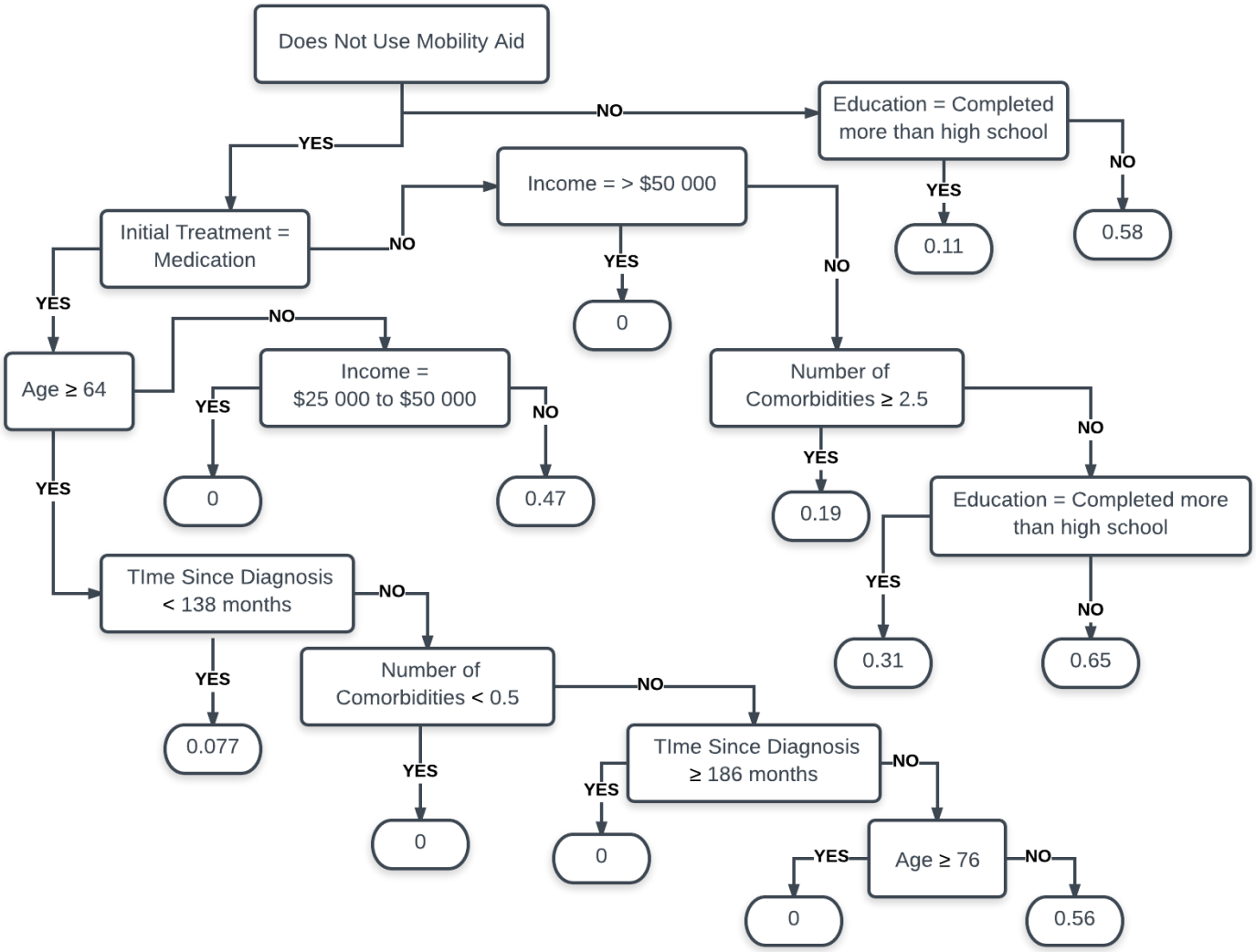


Figure 5-3.Initial classification tree for presence of depressive symptoms

5.6.2.5 Variable Selection for Presence of Depressive Symptoms

The selected variables from multivariable regression, stepwise regression by AIC, initial and pruned CART analyses for predicting the presence of depressive symptoms is presented in Table 5-17. Eight variables were selected from stepwise regression and seven from the initial CART analysis. Two variables were selected from multivariable regression analysis. No variables were

selected by the pruned CART analysis. Initial treatment was selected from all four methods. Use of mobility and initial treatment were selected from three of the four methods. BCVA, number of ocular conditions, number of ocular procedures and glaucoma stage were not selected from any of the methods. Thus, the main predictor variables explaining the presence of depressive symptoms among our patient population were use of mobility aids and initial treatment.

5.6.2.6 Model Assessment for the Presence of Depressive Symptoms

The model with the lowest MAE for the presence of depressive symptoms is stepwise regression model by AIC, with a MAE of 0.30. The plausible models are the models with a MAE of 0.32 or less, which include: initial multivariable regression model, selected multivariable regression model and initial classification tree. From Table 5-18, of the plausible models, the model with the lowest number of predictor variables is the selected multivariable regression model. Therefore, the most promising predictor variables for the presence of depressive symptoms are presented in the model below:

$$\textbf{\textit{Depressive symptoms}} = \alpha + \beta_1 (\textit{use of mobility aid}) + \beta_2 (\textit{initial treatment})$$

5.6.3 Vision-Related Quality of Life

Recall, that the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) was used to assess the vision-related quality of life (VRQoL) among the study population. The overall composite score ranged from 0 to 100, where 100 is the best possible score. On average, the patients reported a composite score of 88.7±12.4, with a minimum average score of 9.8 and maximum of 100. Thus, majority of the patients had a fairly high VRQoL.

5.6.3.1 Unadjusted Effects of Vision-Related Quality of Life

The bivariate analysis for VRQoL with the demographic variables are presented in Table 5-19, and for clinical variables it is presented in Table 5-20. The two demographic variables associated with VRQoL were income ($p = 0.006$) and use of mobility aids ($p < 0.0001$). On average, patients with an income greater than $50 000, are expected to obtain VRQoL that is greater than patients with income less than $25 000 (5.19±1.89, 95% CI = 1.48 to 8.91). Patients who use

mobility aids, on average, are expected to obtain VRQoL that is less than patients who do not use a mobility aids (-11.49±2.37, 95% CI = -16.16 to -6.81).

The two clinical variables associated with VRQoL were BCVA in the worse-seeing eye ($p < 0.0001$) and number of ocular conditions ($p = 0.004$). On average, patients with moderate visual acuity loss (-9.00±1.91, 95% CI = -12.76 to -5.25) and legal blindness (-18.44±2.03, 95% CI = -22.43 to -14.45), are expected to obtain VRQoL that is less than patients with mild visual acuity. On average, for each increase in number of ocular conditions, the expected VRQoL decreases by 2.05±0.71 (95% CI = -3.44 to -0.65).

5.6.3.2 Adjusted Effects of Vision-Related Quality of Life

The estimated coefficients and p-values from the multivariable linear regression analysis with VRQoL as the dependent variable is presented in Table 5-21. The following three demographic and one clinical variables were significantly associated with VRQoL: income ($p = 0.01$), living arrangement ($p = 0.03$), use of mobility aid ($p < 0.0001$) and BCVA in the worse-seeing eye ($p < 0.0001$). When controlling for all variables, living arrangement, use of mobility aids, BCVA in the worse-seeing eye had a negative relationship with VRQoL and income had a positive relationship.

Patients with an income greater than $50 000, on average are expected to obtain VRQoL that is greater than patients income less than $25 000 (3.99±1.63, 95% CI= 0.78 to 7.19). Patients living in a nursing or retirement home, on average, are expected to obtain VRQoL that is lower than patients living at home alone (-22.49±5.24, 95% CI= -32.82 to -12.16). Patients using mobility aids, on average, are expected to obtain VRQoL that is lower than patients not using mobility aids (-7.62±2.15, 95% CI= -11.85 to -3.39). Patients with a moderate visual acuity loss (-8.20±1.92, 95% CI= -11.97 to -4.42) and legal blindness (-17.03±2.02, 95% CI= -21.02 to -13.05), on average, are expected to obtain VRQoL that is lower than patients with mild visual acuity loss.

The overall model was significant ($p < 0.0001$), with a generalized R-squared of 0.40, suggesting that 40% of the variance in NEI VFQ-25 score is explained by this multivariable regression model.

5.6.3.3 Stepwise Regression for Vision-Related Quality of Life

The stepwise regression analysis by AIC for the presence of VRQoL is presented in Table 5-22. The initial model for VRQoL consisted of the 13 predictor variables and had an AIC value of 1167.55. The final model with the lowest AIC value of 1152.89, consisted of the following five predictor variables: income, living arrangement, use of mobility aid, BCVA in the worse-seeing eye and number of ocular conditions.

5.6.3.4 Regression Tree for Vision-Related Quality of Life

The initial regression tree of VRQoL is presented in Figure 5-4, where the data were split (root node) using the variable 'BCVA' and the final split (leaf node) contained the predicted NEI VFQ-25 score ranging from 0 to 100. For example, a patient whose BCVA is categorized as moderate visual acuity loss or legal blindness and uses mobility aid, has a predicted score of 67 (range = 0 to 100). The initial regression tree has five nodes, whereas the pruned tree in Figure 5-5 has only one node.

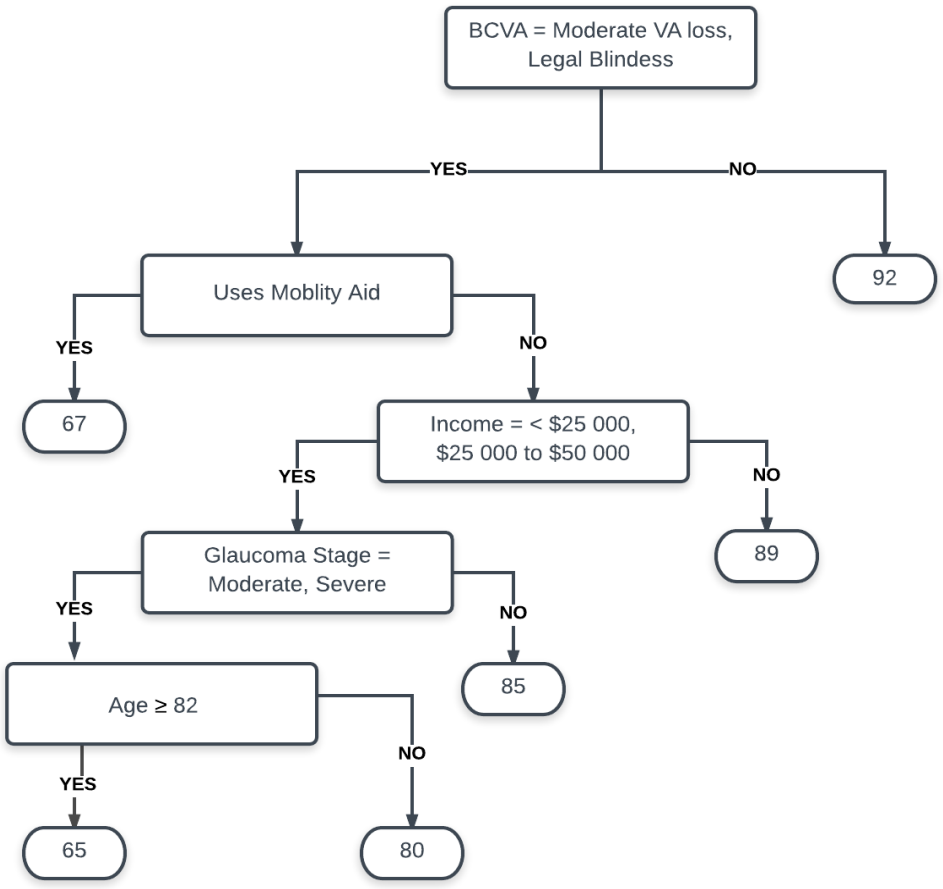


Figure 5-4. Initial regression tree for vision-related quality of life

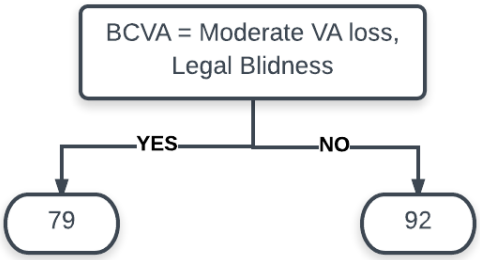


Figure 5-5. Pruned regression tree for vision-related quality of life

5.6.3.5 Variable Selection for Vision-Related Quality of Life

The selected variables from multivariable regression, stepwise regression by AIC, initial and pruned CART analyses for predicting VRQoL is presented in Table 5-23. Five variables were selected from stepwise regression and the initial CART analysis. Four variables were selected from multivariable regression and one variable was selected from the pruned CART analysis. BCVA was selected from all four methods. Income and use of mobility aids were selected from three of the four methods. Sex, education, number of comorbidities, number of ocular procedures, time since diagnosis and initial treatment were not selected from any of the methods. The main predictor variable explaining VRQoL is BCVA in the worse-seeing eye.

5.6.3.6 Model Assessments for Vision-Related Quality of Life

The model with the lowest MAE is the pruned regression tree, with a MAE of 6.77. The plausible models are the models with a MAE of 7.33 or less, which include: initial multivariable regression model, selected multivariable regression model, stepwise regression model and initial regression tree. From Table 5-24, of the plausible models, the model with the lowest number of predictor variables is the pruned regression tree. Therefore, the most promising predictor variables of VRQoL is presented in the mode below:

$$\boldsymbol{VRQoL} = \alpha + \beta_1 (\textit{BCVA in the worse-seeing eye})$$

5.6.4 Preference-Based Health-Related Quality of Life

Recall, that the Time Trade-Off (TTO) technique was used to measure the patients' preference-based HRQoL and the utility value was dichotomized to "not willing to give up any years of life"

and “willing to give up some years of life” (refer to Section 4.5.4). Among the study population, about 71% were not willing to give up any years of life for perfect vision. Thus, majority of the patients had a high preference-based HRQoL.

5.6.4.1 Unadjusted Effects of Preference-Based Health-Related Quality of Life

The bivariate analysis for preference-based HRQoL with the demographic variables are presented in Table 5-25, and for clinical variables in Table 5-26. One demographic and two clinical variables were significantly associated with preference-based HRQoL: education ($p < 0.0001$), legal blindness ($p = 0.009$) and number of ocular conditions ($p = 0.02$). Patients with legal blindness, on average, were more willing to give up some years of like for perfect vision than patients with mild visual acuity loss (OR = 2.81, 95% CI = 1.29 to 6.14). On average, patients were more willing to give up some years of life for perfect vision with increasing number of ocular conditions (OR = 1.37, 95% CI = 1.06 to 1.76).

5.6.4.2 Adjusted Effects of Preference-Based Health-Related Quality of Life

The estimated odds ratio and p-values from the multivariable logistic regression analysis with preference-based HRQoL as the dependent variable is presented in Table 5-27. Two clinical variables were found to be significantly associated with preference-based HRQoL: BCVA in the worse-seeing eye ($p = 0.01$) and number of ocular conditions ($p = 0.04$). No demographic variables were found to be significantly associated.

Patients with legal blindness were more willing to give up some years of life for perfect vision than patients with mild visual acuity loss (OR=3.10, 95% CI= 1.27 to 7.57). Patients were more willing to give up some years of life for perfect vision with increasing number of ocular conditions (OR=1.35, 95% CI= 0.60 to 3.04).

The overall model was not significant ($p = 0.24$), with a pseudo R-squared of 0.09.

5.6.4.3 Stepwise Regression for Preference-Based Health-Related Quality of Life

The stepwise regression analysis by AIC for the presence of preference-based HRQoL is presented in Table 5-28. The initial model for preference-based HRQoL consisted of the 13 predictor variables and had an AIC value of 312.88. The final model with the lowest AIC value of 294.68, consisted of the following four predictor variables: age, education, BCVA worse-seeing eye and number of ocular conditions.

5.6.4.4 Classification Tree for Preference-Based Health-Related Quality of Life

The initial classification tree for preference-based HRQoL is presented in Figure 5-6, where the data were split (root node) using the variable 'age' and the final split (leaf node) contained the predicted probability of giving up any years of life for perfect vision (0 = not willing to give up any years of life). For example, a patient who is ≥ 76 years of age, BCVA is categorized as mild VA loss and has < 2.5 ocular procedures, is predicted to have a 0.11 probability of giving up years of life for perfect vision. The initial classification tree has 15 nodes, and pruning the tree resulted in zero splits.

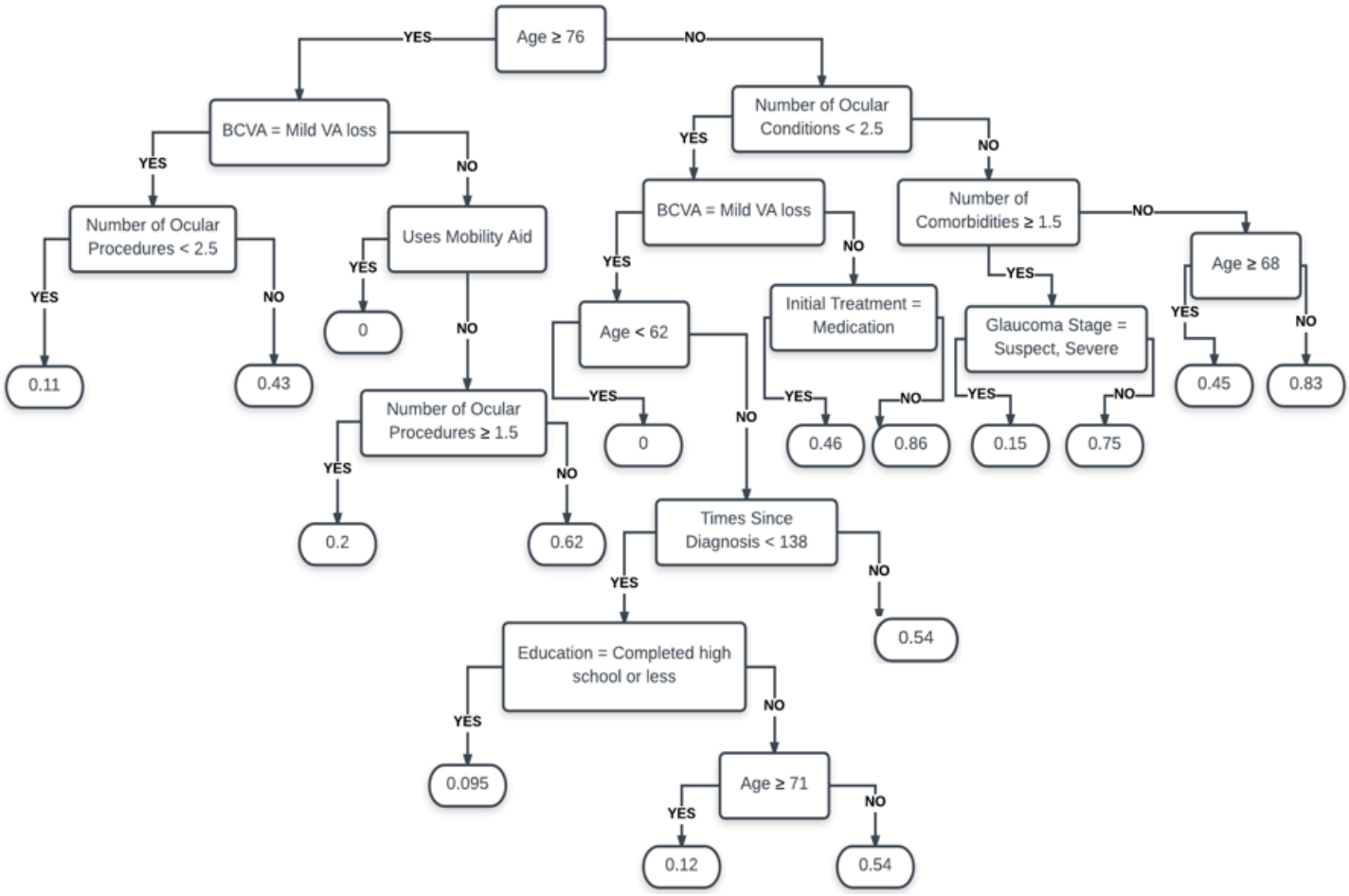


Figure 5-6. Initial classification tree for preference-based Health-Related quality of life

5.6.4.5 Variable Selection for Preference-Based Health-Related Quality of Life

The selected variables from multivariable regression, stepwise regression by AIC, initial and pruned CART analyses for predicting preference-based HRQoL is presented in Table 5-29. Ten variables were selected from the initial CART analysis. Four variables were selected from the stepwise regression analysis. Two variables were selected from the multivariable regression analysis. No variables were selected from the pruned CART analysis. BCVA and number of ocular conditions were selected from two of the four methods. Sex, income and living arrangement were not selected from any of the methods. The main predictor variables explaining

the patients' preference-based HRQoL seems to be BCVA in worse-seeing eye and number of ocular conditions.

5.6.4.6 Model Assessments for Preference-Based Health-Related Quality of Life

The model assessment results for preference-based HRQoL is presented in Table 5-30. The model with the lowest MAE for preference-based HRQoL is initial classification tree, with a MAE of 0.36. The plausible models are the models with a MAE of 0.38 or less, which only included the initial classification tree. However, the initial classification tree is fairly complex with 10 predictor variables and may be overfitting, thus this model needs further assessment:

$$\textbf{\textit{Preference-based HRQoL}} = \alpha + \beta_1 (\textit{age}) + \beta_2 (\textit{education}) + \beta_3 (\textit{use of mobility aid}) + \beta_4 (\textit{BCVA in the worse-seeing eye}) + \beta_5 (\textit{number of comorbidities}) + \beta_6 (\textit{number of ocular conditions}) + \beta_7 (\textit{number of ocular procedures}) + \beta_8 (\textit{glaucoma stage}) + \beta_9 (\textit{time since diagnosis}) + \beta_{10} (\textit{initial treatment})$$

Table 5-1. Demographic characteristics of the study population (N = 250)

Demographic Variables	Mean (SD) or Number of Patients (%)
Age (years)	72.9 (10.2)
Race	
Caucasian	199 (79.6)
East Asian	3 (1.2)
Black	4 (1.6)
First Nations	3 (1.2)
Other	41 (16.4)
Income	
Less than $25 000	87 (37.5)
$25 000 to $50 000	73 (31.5)
Greater than $50 000	72 (31.0)
Education	
Completed high school or less	122 (48.8)
Completed more than high school	128 (51.2)
Living Arrangement	
Home alone	73 (29.2)
Home with others	173 (69.2)
Nursing/Retirement home	4 (1.6)
Use of Mobility Aid	
Does not use mobility aid	222 (88.8)
Uses mobility aid	28 (11.2)

Table 5-2. Clinical characteristics of the study population (N = 250)

Clinical Variables	Mean (SD) or Number of Patients (%)
Best Corrected Visual Acuity	
Mild visual acuity loss	181 (72.4)
Moderate visual acuity loss	37 (14.8)
Legal blindness	32 (12.8)
Number of Comorbidities	1.6 (1.4)
Number of Ocular Conditions	2.1 (1.1)
Number of Ocular Procedures	1.1 (1.0)
Glaucoma Stage	
Suspect	82 (32.8)
Early	65 (26.0)
Moderate	65 (26.0)
Severe	38 (15.2)
Time Since Diagnosis (months)	100.7 (74.5)
Initial Treatment	
Medication	180 (72.0)
Selective Laser Trabeculoplasty	43 (17.2)
No initial treatment	27 (10.8)

Table 5-3. Pre- and post-imputed income values

Missing Variable	Pre-imputed income values *Number of patients (%)*	Post-imputed income values *Number of patients (%)*
Income		
Less than $25 000	87 (37.5)	99 (39.6)
$25 000 to $50 000	73 (31.5)	75 (30.0)
Greater than $50 000	72 (31.0)	76 (30.4)
	N = 232	**N = 250**

Table 5-4. Pearson correlation coefficient for the association between pairs of continuous predictor variables

	Age	Number of Comorbidities	Number of Ocular Conditions	Number of Ocular Procedures	Time Since Diagnosis
Age	1.00				
Number of Comorbidities	0.16	1.00			
Number of Ocular Conditions	0.02	-0.01	1.00		
Number of Ocular Procedures	0.26	0.03	0.16	1.00	
Time Since Diagnosis	0.004	0.05	0.07	0.21	1.00

Table 5-5. Chi-square tests (p-value) for the association between pairs of categorical predictor variables

	Sex	Income	Education	Living Arrangement	Use of Mobility Aid	Best Corrected Visual Acuity	Glaucoma Stage	Initial Treatment
Sex		**0.001**	0.22	**0.02**	0.46	0.14	0.10	0.27
Income			0.49	0.13	0.05	0.22	0.62	0.96
Education				0.06	**0.03**	0.21	0.85	0.89
Living Arrangement					0.68	0.84	0.46	0.81
Use of Mobility Aid						**0.02**	0.79	0.56
Best Corrected Visual Acuity							**0.002**	0.52
Glaucoma Stage								<0.0001
Initial Treatment								

Table 5-6. Results of associations between continuous and categorical predictor variables

Variable	Age	Number of Comorbidities	Number of Ocular Conditions	Number of Ocular Procedures	Time Since Diagnosis
	p-value *mean (SD)*	*p-value* *mean (SD)*	*p-value* *mean (SD)*	*p-value* *mean (SD)*	*p-value* *mean (SD)*
Sex	0.97	**0.01**	0.08	0.89	0.13
Female	72.97 (9.6)	1.77 (1.4)	2.05 (1.0)	1.06 (1.0)	94.88 (73.6)
Male	72.92 (11.1)	1.33 (1.3)	2.29 (1.2)	1.08 (1.1)	109.61 (75.5)
Income	**0.03**	0.75	0.46	0.85	0.88
Less than $25 000	75.01 (10.0)	1.62 (1.3)	2.19 (1.3)	1.11 (0.9)	98.54 (70.8)
$25 000 to $50 000	71.15 (9.2)	1.67 (1.6)	2.01 (0.9)	1.05 (1.0)	100.17 (71.6)
Greater than $50 000	72.04 (11.1)	1.50 (1.4)	2.21 (1.0)	1.03 (1.1)	104.28 (82.5)
Education	0.15	0.33	0.96	0.83	0.11
Completed high school or less	73.89 (10.7)	1.51 (1.4)	2.15 (1.1)	1.08 (1.0)	93.09 (68.5)
Completed more than high school	72.05 (9.8)	1.68 (1.4)	2.14 (1.1)	1.05 (1.0)	108.09 (79.5)
Living Arrangement	**0.0003**	0.94	0.92	0.67	0.91
Home alone	76.82 (9.6)	1.63 (1.3)	2.18 (1.1)	1.14 (1.0)	101.77 (65.9)
Home with others	71.22 (9.8)	1.57 (1.4)	2.13 (1.1)	1.05 (1.0)	100.71 (78.0)
Nursing/Retirement home	77.00 (18.7)	1.75 (1.3)	2.00 (1.2)	0.75 (1.0)	85.50 (89.6)
Use of Mobility Aid	**<0.0001**	0.23	0.20	0.31	0.50
Does not use mobility aid	71.98 (10.1)	1.56 (1.4)	2.11 (1.1)	1.05 (1.0)	99.63 (74.7)
Uses mobility aid	80.61 (8.0)	1.89 (1.5)	2.39 (1.2)	1.25 (0.9)	109.82 (74.1)
Best Corrected Visual Acuity	**0.03**	0.36	**0.006**	0.17	0.16
Mild visual acuity loss	71.90 (10.5)	1.61 (1.4)	2.01 (1.0)	0.99 (1.0)	100.60 (71.3)
Moderate visual acuity loss	76.30 (9.4)	1.78 (1.2)	2.43 (1.4)	1.24 (1.0)	85.30 (66.0)
Legal blindness	75.03 (8.3)	1.31 (1.5)	2.56 (1.1)	1.28 (1.2)	119.63 (96.8)
Glaucoma Stage	**0.0009**	0.47	0.97	**0.04**	0.07
Suspect	69.45 (11.1)	1.59 (1.3)	2.15 (1.1)	0.84 (0.8)	83.24 (63.5)
Early	75.23 (9.5)	1.72 (1.6)	2.17 (1.1)	1.26 (1.1)	106.55 (94.2)
Moderate	73.35 (8.5)	1.66 (1.4)	2.09 (1.0)	1.03 (1.0)	109.23 (63.5)
Severe	75.90 (10.4)	1.23 (1.2)	2.18 (1.2)	1.29 (1.2)	114.24 (72.3)
Initial Treatment	0.17	0.12	0.19	**0.001**	**0.0002**
Medication	73.57 (10.1)	1.50 (1.4)	2.22 (1.1)	1.21 (1.1)	111.50 (77.3)
Selective Laser Trabeculoplasty	72.40 (9.2)	1.70 (1.6)	1.88 (1.1)	0.67 (0.8)	86.54 (58.6)
No initial treatment	69.70 (12.3)	2.07 (1.1)	2.07 (1.0)	0.74 (0.8)	51.93 (54.2)

Table 5-7. Unadjusted effects of demographic variables with social support and community integration

Demographic Variables	Coefficient	P-value
Age (years)	-0.17	**<0.0001**
Sex		**<0.0001**
Female	*Ref*	
Male	-3.18	<0.0001
Income		**<0.0001**
Less than $25 000	*Ref*	
$25 000 to $50 000	2.17	0.005
Greater than $50 000	2.95	<0.0001
Education		0.62
Completed high school or less	*Ref*	
Completed more than high school	0.18	0.78
Living Arrangement		**<0.0001**
Home alone	*Ref*	
Home with others	-1.97	0.004
Nursing/Retirement home	-9.26	<0.0001
Use of Mobility Aid		**<0.0001**
Does not use mobility aid	*Ref*	
Uses mobility aid	-4.96	<0.0001

Table 5-8. Unadjusted effects of clinical variables with social support and community integration

Clinical Variables	Coefficient	P-Value
Best Corrected Visual Acuity		0.25
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	-2.23	**0.01**
Legal blindness	-1.60	0.09
Number of Comorbidities	-0.08	0.74
Number of Ocular Conditions	-0.07	0.82
Number of Ocular Procedures	-0.33	0.29
Glaucoma Stage		0.74
Suspect	*Ref*	
Early	-1.08	0.19
Moderate	-0.50	0.54
Severe	-1.19	0.23
Time Since Diagnosis (months)	0.0002	0.96
Initial Treatment		0.44
Medication	*Ref*	
Selective Laser Trabeculoplasty	0.39	0.65
No initial treatment	1.67	0.11

Table 5-9. Adjusted effects for social support and community integration

Variables	Coefficient	P-value
Age (years)	-0.15	**<0.0001**
Sex		**<0.0001**
Female	*Ref*	
Male	-3.28	<0.0001
Income		**<0.0001**
Less than $25 000	*Ref*	
$25 000 to $50 000	1.34	0.04
Greater than $50 000	3.07	<0.0001
Education		0.76
Completed high school or less	*Ref*	
Completed more than high school	0.05	0.92
Living Arrangement		**<0.0001**
Home alone	*Ref*	
Home with others	-2.58	<0.0001
Nursing/Retirement home	-7.92	<0.0001
Use of Mobility Aid		**0.003**
Does not use mobility aid	*Ref*	
Uses mobility aid	-2.63	0.003
Best Corrected Visual Acuity		0.15
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	-1.59	**0.04**
Legal blindness	-0.76	0.35
Number of Comorbidities	-0.04	0.83
Number of Ocular Conditions	0.22	0.37
Number of Ocular Procedures	0.04	0.89
Glaucoma Stage		0.22
Suspect	*Ref*	
Early	0.54	0.45
Moderate	0.42	0.56
Severe	1.34	0.13
Time Since Diagnosis (months)	0.002	0.58
Initial Treatment		0.09
Medication	*Ref*	
Selective Laser Trabeculoplasty	0.50	0.49
No initial treatment	1.41	0.13

Table 5-10. Stepwise regression analysis for social support and community integration

Model ID	Eliminated Variable	AIC
1 (initial)		706.19
2	Glaucoma Stage	702.25
3	Initial Treatment	699.72
4	Number of Comorbidities	697.72
5	Education	695.73
6	Time Since Diagnosis	693.83
7	Number of Ocular Procedures	692.05
8	Number of Ocular Conditions	690.99
9	Best Corrected Visual Acuity	690.61

Table 5-11. Variable selection for social support and community integration

	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Model Selection by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Age	**X**	**X**	**X**	**X**	**X**
Sex	**X**	**X**	**X**	**X**	**X**
Income	**X**	**X**	**X**	**X**	
Education	**X**				
Living Arrangement	**X**	**X**	**X**	**X**	
Use of Mobility Aid	**X**	**X**	**X**	**X**	**X**
BCVA in Worse-Seeing Eye	**X**			**X**	
No. of Comorbidities	**X**				
No. of Ocular Conditions	**X**				
No. of Ocular Procedures	**X**				
Glaucoma Stage	**X**			**X**	
Time Since Diagnosis	**X**			**X**	
Initial Treatment	**X**				
No. of Selected Variables	13	5	5	8	3

Table 5-12. Model assessments from leave-one-out cross validation for social support and community integration models

	Baseline Model (intercept only)	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Regression Model by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Mean Absolute Error	3.99	3.32	3.23	3.21	3.87	3.90
Standard Error	0.19	0.16	0.15	0.16	0.20	0.19
Standard Deviation	3.02	2.52	2.40	2.45	3.11	3.02

Table 5-13. Unadjusted effects of demographic variables for the presence of depressive symptoms

Demographic Variables	Odds Ratio	P-value
Age (years)	0.99	0.51
Sex		0.31
Female	*Ref*	
Male	0.52	0.05
Income		**0.04**
Less than $25 000	*Ref*	
$25 000 to $50 000	0.69	0.32
Greater than $50 000	0.43	0.04
Education		**<0.0001**
Completed high school or less	*Ref*	
Completed more than high school	0.50	0.03
Living Arrangement		**0.04**
Home alone	*Ref*	
Home with others	0.58	0.10
Nursing/Retirement home	2.65	0.35
Use of Mobility Aid		**<0.0001**
Does not use mobility aid	*Ref*	
Uses mobility aid	3.31	0.004

Table 5-14. Unadjusted effects of clinical variables for the presence of depressive symptoms

Clinical Variables	Odds Ratio	P-Value
Best Corrected Visual Acuity		0.47
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	1.76	0.16
Legal blindness	1.17	0.74
Number of Comorbidities	0.91	0.40
Number of Ocular Conditions	1.14	0.37
Number of Ocular Procedures	1.00	0.95
Glaucoma Stage		0.74
Suspect	*Ref*	
Early	0.44	**0.06**
Moderate	0.75	0.46
Severe	0.73	0.50
Time Since Diagnosis (months)	1.00	0.70
Initial Treatment		**<0.0001**
Medication	*Ref*	
Selective Laser Trabeculoplasty	2.08	0.06
No initial treatment	2.40	0.05

Table 5-15. Adjusted effects for the presence of depressive symptoms

Variables	Odds Ratio	P-value
Age (years)	0.97	0.07
Sex		0.09
Female	*Ref*	
Male	0.49	0.08
Income		0.15
Less than $25 000	*Ref*	
$25 000 to $50 000	0.82	0.64
Greater than $50 000	0.57	0.23
Education		0.09
Completed high school or less	*Ref*	
Completed more than high school	0.60	0.16
Living Arrangement		0.41
Home alone	*Ref*	
Home with others	0.59	0.17
Nursing/Retirement home	4.68	0.18
Use of Mobility Aid		**0.006**
Does not use mobility aid	*Ref*	
Uses mobility aid	4.37	0.004
Best Corrected Visual Acuity		0.80
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	1.81	0.23
Legal blindness	0.83	0.73
Number of Comorbidities	0.83	0.18
Number of Ocular Conditions	1.20	0.26
Number of Ocular Procedures	1.13	0.52
Glaucoma Stage		0.71
Suspect	*Ref*	
Early	0.60	0.31
Moderate	1.01	0.99
Severe	1.09	0.89
Time Since Diagnosis (months)	1.00	0.15
Initial Treatment		**0.01**
Medication	*Ref*	
Selective Laser Trabeculoplasty	3.52	0.007
No initial treatment	3.24	0.046

Table 5-16. Stepwise regression for the presence of depressive symptoms

Model ID	Eliminated Variable	AIC
1 (initial)	None	258.39
2	Glaucoma Stage	253.84
3	Income	251.44
4	Number of Ocular Procedures	249.69
5	Best Corrected Visual Acuity	248.03
6	Number of Ocular Conditions	247.71

Table 5-17. Variable selection results for presence of depressive symptoms

	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Model Selection by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Age	**X**		**X**	**X**	
Sex	**X**		**X**		
Income	**X**			**X**	
Education	**X**		**X**	**X**	
Living Arrangement	**X**		**X**		
Use of Mobility Aid	**X**	**X**	**X**	**X**	
BCVA in Worse-Seeing Eye	**X**				
No. of Comorbidities	**X**		**X**	**X**	
No. of Ocular Conditions	**X**				
No. of Ocular Procedures	**X**				
Glaucoma Stage	**X**				
Time Since Diagnosis	**X**		**X**	**X**	
Initial Treatment	**X**	**X**	**X**	**X**	
No. of Selected Variables	13	2	8	7	0

Table 5-18. Model assessments from leave-one-out cross validation for presence of depressive symptoms

	Baseline Model (Intercept only)	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Regression Model by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Mean Absolute Error	0.34	0.31	0.32	0.30	0.32	0.34
Standard Error	0.02	0.02	0.02	0.02	0.02	0.02
Standard Deviation	0.24	0.27	0.25	0.26	0.30	0.24

Table 5-19. Unadjusted effects of demographic variables for vision-related quality of life

Demographic Variables	Coefficient	P-value
Age (years)	-0.07	0.35
Sex		0.88
Female	*Ref*	
Male	0.08	0.96
Income		**0.006**
Less than $25 000	*Ref*	
$25 000 to $50 000	2.28	0.23
Greater than $50 000	5.19	0.006
Education		0.114
Completed high school or less	*Ref*	
Completed more than high school	1.58	0.31
Living Arrangement		0.12
Home alone	*Ref*	
Home with others	-0.58	0.73
Nursing/Retirement home	-23.23	<0.0001
Use of Mobility Aid		**<0.0001**
Does not use mobility aid	*Ref*	
Uses mobility aid	-11.49	<0.0001

Table 5-20. Unadjusted effects of clinical variables for vision-related quality of life

Clinical Variables	Coefficient	P-Value
Best Corrected Visual Acuity		**<0.0001**
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	-9.00	<0.0001
Legal blindness	-18.44	<0.0001
Number of Comorbidities	0.43	0.45
Number of Ocular Conditions	-2.05	**0.004**
Number of Ocular Procedures	-0.59	0.45
Glaucoma Stage		0.225
Suspect	*Ref*	
Early	1.56	0.45
Moderate	0.59	0.77
Severe	-3.61	0.14
Time Since Diagnosis (months)	0.006	0.60
Initial Treatment		0.36
Medication	*Ref*	
Selective Laser Trabeculoplasty	0.46	0.83
No initial treatment	-2.86	0.26

Table 5-21. Adjusted effects for vision-related quality of life

Variables	Coefficient	P-value
Age (years)	0.07	0.33
Sex		0.45
Female	*Ref*	
Male	1.04	0.45
Income		**0.01**
Less than $25 000	*Ref*	
$25 000 to $50 000	0.87	0.59
Greater than $50 000	3.99	0.02
Education		0.64
Completed high school or less	*Ref*	
Completed more than high school	0.40	0.76
Living Arrangement		**0.03**
Home alone	*Ref*	
Home with others	-1.29	0.38
Nursing/Retirement home	-22.49	<0.0001
Use of Mobility Aid		**<0.0001**
Does not use mobility aid	*Ref*	
Uses mobility aid	-7.62	<0.0001
Best Corrected Visual Acuity		**<0.0001**
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	-8.20	<0.0001
Legal blindness	-17.03	<0.0001
Number of Comorbidities	0.44	0.36
Number of Ocular Conditions	-1.02	0.09
Number of Ocular Procedures	-0.27	0.67
Glaucoma Stage		0.88
Suspect	*Ref*	
Early	1.13	0.52
Moderate	0.16	0.93
Severe	0.99	0.65
Time Since Diagnosis (months)	0.006	0.50
Initial Treatment		0.20
Medication	*Ref*	
Selective Laser Trabeculoplasty	-0.64	0.72
No initial treatment	-2.55	0.27

Table 5-22. Stepwise regression analysis for vision-related quality of life

Model ID	Eliminated Variable	AIC
1 (initial)	None	1167.55
2	Glaucoma Stage	1162.04
3	Initial Treatment	1159.97
4	Number of Ocular Procedures	1157.98
5	Education	1156.01
6	Number of Comorbidities	1154.71
7	Sex	1153.45
8	Time Since Diagnosis	1153.03
9	Age	1152.89

Table 5-23. Variable selection for vision-related quality of life

	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Model Selection by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Age	**X**			**X**	
Sex	**X**				
Income	**X**	**X**	**X**	**X**	
Education	**X**				
Living Arrangement	**X**	**X**	**X**		
Use of Mobility Aid	**X**	**X**	**X**	**X**	
BCVA in Worse-Seeing Eye	**X**	**X**	**X**	**X**	**X**
No. of Comorbidities	**X**				
No. of Ocular Conditions	**X**		**X**		
No. of Ocular Procedures	**X**				
Glaucoma Stage	**X**			**X**	
Time Since Diagnosis	**X**				
Initial Treatment	**X**				
No. of Selected Variables	13	4	5	5	1

Table 5-24. Model assessments from leave-one-out cross validation for vision-related quality of life

	Baseline Model (Intercept only)	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Regression Model by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Mean Absolute Error	7.73	7.23	6.86	6.95	7.25	6.77
Standard Error	0.61	0.53	0.52	0.51	0.58	0.56
Standard Deviation	9.69	8.32	8.14	8.07	9.12	8.83

Table 5-25. Unadjusted effects of demographic variables with preference-based HRQoL

Demographic Variables	Odds Ratio	P-value
Age (years)	0.98	0.96
Sex		0.96
Female	*Ref*	
Male	1.32	0.33
Income		0.42
Less than $25 000	*Ref*	
$25 000 to $50 000	0.75	0.40
Greater than $50 000	0.76	0.44
Education		**<0.0001**
Completed high school or less	*Ref*	
Completed more than high school	1.54	0.13
Living Arrangement		0.23
Home alone	*Ref*	
Home with others	1.58	0.16
Nursing/Retirement home	1.10	0.94
Use of Mobility Aid		0.83
Does not use mobility aid	*Ref*	
Uses mobility aid	0.62	0.32

Table 5-26. Unadjusted effects of clinical variables with preference-based HRQoL

Clinical Variables	Coefficient	P-Value
Best Corrected Visual Acuity		0.22
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	1.70	0.17
Legal blindness	2.81	**0.009**
Number of Comorbidities	0.87	0.19
Number of Ocular Conditions	1.37	**0.02**
Number of Ocular Procedures	1.01	0.97
Glaucoma Stage		0.16
Suspect	*Ref*	
Early	1.00	0.98
Moderate	1.20	0.61
Severe	1.03	0.95
Time Since Diagnosis (months)	1.00	0.78
Initial Treatment		0.27
Medication	*Ref*	
Selective Laser Trabeculoplasty	1.72	
No initial treatment	0.97	0.95

Table 5-27. Adjusted effects for preference-based HRQoL

Variables	Odds Ratio	P-value
Age (years)	0.98	0.28
Sex		0.65
Female	*Ref*	
Male	1.14	0.69
Income		0.24
Less than $25 000	*Ref*	
$25 000 to $50 000	0.72	0.40
Greater than $50 000	0.64	0.28
Education		0.20
Completed high school or less	*Ref*	
Completed more than high school	1.50	0.19
Living Arrangement		0.32
Home alone	*Ref*	
Home with others	1.53	0.24
Nursing/Retirement home	1.30	0.84
Use of Mobility Aid		0.19
Does not use mobility aid	*Ref*	
Uses mobility aid	0.48	0.20
Best Corrected Visual Acuity		**0.01**
Mild visual acuity loss	*Ref*	
Moderate visual acuity loss	2.11	0.09
Legal blindness	3.10	0.01
Number of Comorbidities	0.88	0.27
Number of Ocular Conditions	1.35	**0.04**
Number of Ocular Procedures	1.02	0.91
Glaucoma Stage		0.83
Suspect	*Ref*	
Early	1.09	0.85
Moderate	1.35	0.46
Severe	0.90	0.84
Time Since Diagnosis (months)	1.00	0.95
Initial Treatment		0.39
Medication	*Ref*	
Selective Laser Trabeculoplasty	1.98	0.09
No initial treatment	1.19	0.76

Table 5-28. Stepwise regression analysis for preference-based HRQoL

Model ID	Eliminated Variable	AIC
1 (initial)	None	312.88
2	Glaucoma Stage	307.74
3	Income	305.19
4	Living Arrangement	302.46
5	Time Since Diagnosis	300.46
6	Number of Ocular Procedures	298.47
7	Sex	296.56
8	Use of Mobility Aid	295.64
9	Number of Comorbidities	295.11
10	Initial Treatment	294.68

Table 5-29. Variable selection results for predicting preference-based HRQoL

	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Model Selection by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Age	**X**		**X**	**X**	
Sex	**X**				
Income	**X**				
Education	**X**		**X**	**X**	
Living Arrangement	**X**				
Use of Mobility Aid	**X**			**X**	
BCVA in Worse-Seeing Eye	**X**	**X**	**X**	**X**	
No. of Comorbidities	**X**			**X**	
No. of Ocular Conditions	**X**	**X**	**X**	**X**	
No. of Ocular Procedures	**X**			**X**	
Glaucoma Stage	**X**			**X**	
Time Since Diagnosis	**X**			**X**	
Initial Treatment	**X**			**X**	
No. of Selected Variables	13	2	4	10	0

Table 5-30. Model assessments from leave-one-out cross validation for preference-based HRQoL

	Baseline Model (Intercept only)	Initial Multivariable Regression Model	Selected Multivariable Regression Model	Stepwise Regression Model by AIC	Initial Classification and Regression Tree	Pruned Classification and Regression Tree
Mean Absolute Error	0.42	0.41	0.41	0.40	0.36	0.42
Standard Error	0.01	0.02	0.01	0.01	0.02	0.01
Standard Deviation	0.19	0.24	0.21	0.22	0.31	0.19

Chapter 6

6 Discussion

This chapter begins with a statement of the overall goal of our research study (Section 6.1). Section 6.2 presents a summary of the study results. Following is the interpretation of the study results coinciding with each study objective (Section 6.3). Next, the strengths and limitations (Section 6.4) of the study are presented. The future directions are discussed in Section 6.5. Lastly, the conclusions are presented in Section 6.6.

6.1 Overall Goal of Study

The overall goal of our research study was to identify predictor variables that are most strongly associated with four PROs: social support and community integration; presence of depressive symptoms; VRQoL; and preference-based HRQoL. This was accomplished through rigorous methodologies including inferential statistics and machine learning techniques. Identifying important drivers of PROs can support ophthalmologists to better manage and treat glaucoma patients. In addition to the clinical importance of this study, the proposed methodology can be used for future research. Our research study highlights rigorous methodology that goes beyond interpreting results based on statistical significance.

6.2 Summary of Study Results

Overall, the patients in our study are satisfied with their care and treatment. Patients reported low depressive symptoms, moderate social support and community integration, high VRQoL and preference-based HRQoL.

The patients were spread across a wide age range between 40 and 93 years of age, with a mean age of about 73 years old. Forty percent of the patients had an income lower than $25 000, and about 49% completed high school or less, thus there was not much variability in income and education levels. In terms of their clinical outcomes, about 72% experienced mild visual acuity loss; thus, their visual functioning was not greatly debilitated. The time since diagnosis ranged widely from one month to about 42 years, with an average time of about eight years. On average,

the patients had about two other comorbidities and two other ocular conditions (excluding glaucoma) and had about one prior ocular procedure performed.

In our patient population, use of mobility aids was a common predictor variable identified for three of the PROs: social support and community integration, presence of depressive symptoms and VRQoL. BCVA in the worse-seeing eye was a common predictor variable identified for three of the PROs: social support and community integration, VRQoL and preference-based HRQoL. Income and living arrangements were common predictor variables identified for social support and community integration and VRQoL. Thus, across all PROs, clinical predictors that are routinely collected (BCVA) during a typical comprehensive eye exam did not seem to have as much of an influence as the variables that were not typically collected (use of mobility aids, income and living arrangements).

Understanding the predictor variables of important PROs may help ophthalmologists identify patients who are at a greater risk or who would most benefit from services that could improve their disease management. For instance, if an ophthalmologist can identify a patient who may need social support and who is unable to perform activities of daily living due to their glaucoma progression, then ophthalmologists would consider referral of these patients for necessary support and services. The developed models could help ophthalmologists be more aware of their patients' ocular and non-ocular needs. This is particularly important for this patient population, since our study findings suggest that many of the factors that are driving PROs are not clinical. Our results indicate that ensuring that the patient has an adequate support system and access to services to help them adapt to loss of their visual functioning could have a larger impact on improving PROs than providing clinical management alone. In addition, the results obtained can be a guide for future ophthalmic research in assessing predictor variables of important PROs. The developed models (refer to Section 5.6) may be a useful tool for ophthalmologists, researchers, health economists and policy makers for better tailored glaucoma management.

6.3 Interpretation of Study Results

6.3.1 Social Support and Community Integration

The first objective of our research study was to assess social support and community integration as measured by the Community Integration Questionnaire (CIQ), and determine which clinical and/or demographic variables impact the overall score.

Patients in our research study scored moderately high on the CIQ scale, with an average score of 17.9±5.0, representing moderate social support and community integration. In comparison, Hirsh et al. (2011) conducted a cross-sectional study which included 751 adults with different physical disabilities (spinal cord injury, multiple sclerosis, limb loss and muscular dystrophy), and reported, on average, a similar total score of 17.1±5.1[101]. However, in comparison to our research study, the participants from Hirsh et al.'s (2011) study were, on average, younger (50.9±13.5 years, range: 18 to 91) and a greater number had completed more than high school (84%)[101]. Singh et al. (2015) conducted a study among 30 geriatric patients and reported a total score of 22.9±5.0, which is slightly higher than our study population[109]. On average, the study population of Singh et al. (2015) was similar in age (73 years; range: 65 to 90) to our study population[109]. However, the proportion of patients who were over 75 years of age was less (33%) than the proportion in our study population (41%). Patients over 75 years of age may be less able to participate in the community and lack social support than the younger patients. To our knowledge, ophthalmology research and ophthalmic practice do not assess the patient's social support and community integration needs.

We found age, sex, income, living arrangement and use of mobility aids to be the most promising predictor variables of social support and community integration. Specifically, increasing age, being a male, and living at home with others or in a nursing/retirement home, predicted lower social support and community integration. Income above $25 000 was predictive of greater social support and community integration. Considering the absolute values of the regression coefficients, living in a nursing or retirement home (β = -7.92) and having an income greater than $50 000 ($\beta$ = 3.07) are expected to have the strongest effects on the patient's level of social support and community integration. However, among our study population only 1.6% (n = 4) were living in a nursing or retirement home. Our findings suggest that these patients are less

functional within their community and need the support of others (i.e., spouse, family or caregiver). For instance, patients who use mobility aids may require assistance to perform their daily activities such as shopping and going to visit family and friends. To be more confident in the results, a larger representation of patients living in a nursing or retirement home would be required.

Overall, the moderate level of social support and community integration among our study population was not surprising, since only a small proportion of our population had severe glaucoma. This may reflect the practice pattern of the ophthalmologist who manages patients at all stages of glaucoma and institutes care for preventing their disease from becoming advanced. Thus, inclusion of more equal proportion of patients within each glaucoma stage and living arrangement category may strengthen some associations.

6.3.2 Presence of Depressive Symptoms

The second objective of our research study was to assess the presence of depressive symptoms as measured by the Patient Health Questionnaire-9 (PHQ-9), and determine which clinical and/or demographic variables impact the presence or absence of depressive symptoms.

Depression has been reported to be higher in individuals with chronic illnesses and among elderly people. Glaucoma is a chronic ocular disease that is most prevalent among elderly people and due to the progression of vision loss, it is likely that patients experience depressive symptoms[182]. Among our study population, about 21% reported having depressive symptoms. Simon et al. (2008) used the Geriatric Depression Scale-15 and found that depression was more prevalent with increasing glaucoma severity[113]. Although the majority of our study population did not present with depressive symptoms, it is important to note that only about 15% of the patients were diagnosed with severe glaucoma. Thus, having a study population that included a greater number of patients with advanced disease may provide more accurate effect estimates. Assessing depressive symptoms among glaucoma patients and identifying associated factors are still important in providing better care to improve the patients' HRQoL as knowledge of the diagnosis itself and its treatment may be a source of depression for some patients.

Our results suggest that use of mobility aids and initial treatment were the most promising predictor variables of the presence of depressive symptoms. Patients who used mobility aids were about four times more likely to report the presence of depressive symptoms than patients who did not use mobility aids. It was predicted that medication use would be more burdensome for the patient, due to the inconvenience of the medication regimen and well established reports of poor patient compliance. However, our study results revealed that patients whose initial treatment was selective laser trabeculoplasty (SLT), or who had no initiations of treatment, were both more than about three times more likely to report having depressive symptoms compared to patients whose initial treatment was medication. This study finding was surprising for a number of reasons. Published studies have shown that both SLT and medication are known to be effective in lowering IOP in patients, and literature supports SLT as an effective initial treatment thus preventing, or delaying, the need for medical therapy[183]. Possible reasons for this finding include: patients who did not receive medical management for glaucoma had, by chance, other underlying causes for depressive symptoms; the patients who did not receive medical management had protective factors against depression; patients whose initial treatment was medication were more secure in the perception that they were actively participating in their disease management; the need for chronic medical therapy is not as burdensome for some patients as published studies have suggested; and lastly, a larger, more diverse sample size may be required to accurately report on this finding.

To our knowledge no previous studies among glaucoma patients have used the PHQ-9 to assess depressive symptoms. However, Wilson et al. (2002) did conduct a study using the Center for Epidemiologic Studies Depression Scale and Composite International Diagnostic Interview Short Form, among patients with glaucoma and without glaucoma[182]. Wilson et al., (2002) concluded that patients with glaucoma did not report being more depressed than patients without glaucoma[182]. On the other hand, a multicentre prospective case-control study reported that patients with POAG had a higher prevalence of depression than the sex- and age-matched control group[92]. In addition, a study conducted among glaucoma patients in a Turkish population, found that the presence of depression was associated with lower QoL scores[111]. Furthermore, a study that used the Hamilton Depression Rating Scale among Singaporean patients with glaucoma, found that 30% of their study population had depression, and found that female sex and

worsening clinical outcomes of the eye were significant factors associated with depression[16]. Supporting our study findings, Wilson et al. (2002) reported that clinical outcome measures such as visual acuity, visual field severity and use of topical medication were not strongly predictive of depression among glaucoma patients[182].

6.3.3 Vision-related Quality of Life

The third objective of our study was to assess vision-related quality of life (VRQoL) as measured by the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), and determine which clinical and/or demographic variables impacted the composite score, in glaucoma suspects and patients diagnosed with glaucoma.

The VRQoL of our study population was reported to be high, with a composite score of 88.7±12.4. As previously stated, there were only 15% of patients who were diagnosed with severe glaucoma in our study population. In contrast, a study conducted among a Turkish population, reported a lower composite score of (66.4±19.3)[184]. However, the mean age in the Turkish population was younger (60.9±14.5 years) and only 9.8% were diagnosed with glaucoma; the rest of the patients were diagnosed with either cataract (57.4%), diabetic retinopathy (13.2%), age-related macular degeneration (11.4%) or degenerative myopia (8.2%)[184]. Karadeniz et al. (2017) reported a composite score of 86.4±7.0 among glaucoma patients and found significant correlation between BCVA and VRQoL[185]. Although, on average, the age of the study population reported by Karadeniz et al. (2017) was younger (64.9±10.5 years) than the age of our study population, the composite score obtained in both study populations were similar.

Previous studies have assessed the VRQoL of glaucoma patients using the NEI VFQ-25. Carreras et al. (2017) found that patients with moderate to severe glaucoma reported significantly lower NEI VFQ-25 scores than patients with normal eyes[186]. Cahill et al. (2005) reported that NEI VFQ-25 scores, among a group of patients with low vision, were negatively correlated with increasing age and duration of vision loss[187]. A study among a Swedish population used a Swedish translation of the NEI VFQ-25 to assess VRQoL and concluded that the scores were associated with clinical characteristics such as visual acuity and visual field loss and patients with no visual impairment scored higher than patients with visual impairment[188]. Similarly, our

results suggest that the best possible predictor variable of VRQoL was BCVA in the worse-seeing eye. Specifically, the absolute values of the multivariable regression coefficients suggest that legal blindness *(β = -17.03*) and moderate visual acuity loss *(β = -8.20*) are expected to have a larger decrease on VRQoL, compared to patients with mild visual acuity loss. In addition, Murata et al. (2015) confirm our results, as they also reported BCVA in the worse-eye as the most important variable for VRQoL[189]. Takahashi et al. (2016) also found significant associations between visual function impairment and VRQoL[190]. In addition, Sun et al. (2016) reported that patients with visual defects in the better eye were more likely to have lower VRQoL scores[191]. Thus, vision-specific clinical outcome measures are important predictor variables of VRQoL.

6.3.4 Preference-based Health-Related Quality of Life

The fourth objective of our research study was to assess the preference-based HRQoL as measured by the Time Trade-Off technique (TTO) and determine which clinical and/or demographic variables impact the utility values in glaucoma suspects and patients diagnosed with glaucoma.

Among our study population only about 10% had a low visual acuity with low vision reporting either counting fingers (CF), hand motion (HM), light perception (LP) or no light perception (NLP). Thus, very few patients reported low TTO utility values. Previous studies reported associations between preference-based HRQoL and visual acuity. Brown (1999) concluded that preference-based HRQoL decreases as the vision in the better-seeing eye decreases[87]. Brown et al. (1999) reported that patients with a poor visual acuity value (i.e., counting fingers) were willing to give up more years of their remaining life compared to patients with a better visual acuity (i.e., 20/20)[123].

Recall from Section 2.7.4 that utility values are rated on a scale between 0 (death) and 1 (perfect health). The utility value reported by our patient population, on average was 0.91. About 71% of the patients reported a perfect utility value of 1, meaning that majority of the patients were not willing to give up any years of life for perfect vision. This finding may, in part, be due to the relatively small number of severe glaucoma patients in the study population (15%). Likewise, Jampel et al. (2002) reported a high preference-based HRQoL (utility value = 0.93) among

patients diagnosed with glaucoma[192]. The glaucoma patients in Jampel et al.'s (2002) study were similar in age to our study population (71.8±11.2 years) and majority were Caucasian (76%)[192].

A low mean TTO utility value of 0.64 was reported among a group of Indian glaucoma patients, representing a poorer preference-based HRQoL[96]. Another study among a Chinese population reported a mean utility value of 0.88[124]. Since our study population was about 80% Caucasian, further investigation would be interesting in a more diverse Canadian population to evaluate the effect of race in a country which has access to a universal health care system.

Aspinall et al. (2008) reported that only 17% of the patients were willing to consider trading their remaining years of life for perfect vision[125]. Among our study population, about 30% were willing to consider trading their remaining years of life for perfect vision. Although Aspinall et al. (2008) did not include patients with other ocular comorbidities and had a smaller sample size (n = 72), similar to our research study, only a minority of patients were willing to trade their years of life for perfect vision.

The results of our study found that the most promising predictor variables of preference-based HRQoL were: age, education, use of mobility aids, BCVA in the worse-seeing eye, number of comorbidities, number of ocular conditions, number of ocular procedures, glaucoma stage, time since diagnosis and initial treatment. To avoid overfitting, the TTO model would benefit from further assessment, with a larger population of diverse glaucoma severity groups.

Similar to our study findings, previous studies reported both clinical and demographic associations with preference-based HRQoL. Like our study, Sharma et al. (2000) included patients with various ocular conditions and determined that preference-based HRQoL was significantly associated with only BCVA in the better-seeing eye[138]. Kobelt et al. (2006) reported that clinical variables such as total visual acuity, visual acuity in the better-seeing eye were significantly correlated with preference-based HRQoL and patients with severe damage reported poorer HRQoL[193]. However, very few patients in our study population had severe glaucomatous damage. In addition, to the commonly reported association between preference-based HRQoL and visual acuity loss, Gupta et al. (2005) also found significant associations between preference-based HRQoL and educational status[96]. Our study findings also found education to be

predictive of preference-based HRQoL. Likewise, Guedes et al. (2014) reported that higher education tended to predict higher preference-based HRQoL [150]. Zhang et al. (2015) also reported that preference-based HRQoL was related to education level and employment status[151]. Contrary to our findings, Brown (1999) found that age, level of education, gender, race, length of time of visual loss and number of comorbidities did not significantly affect preference-based HRQoL[87]. Brown (1999) only included patients who had a visual loss of 20/40 or worse, whereas in our study included patients with visual loss better than 20/40.

It is important to note that the mentioned studies only performed multivariable regression analysis to determine which variables were associated with preference-based HRQoL, whereas our research study performed multivariable regression analysis, stepwise regression by AIC and variable selection using CART to identify the most promising predictor variables of preference-based HRQoL.

6.3.5 Models for Predicting Patient-Reported Outcomes

The final objective of this study was to develop models for predicting social support and community integration, presence of depressive symptoms, VRQoL and preference-based HRQoL based on clinical and/or demographic variables, and validate the resulting models.

A total of 13 predictor variables were included in the initial model for analysis for each PRO. After performing three model selection methods (multivariable regression, stepwise regression by AIC, and CART) and assessing the model performance using LOOCV, the most promising predictor variables to be included in the final model for each PRO were identified to be the following:

Social support and community integration: age, sex, income, living arrangement and use of mobility aids

Presence of depressive symptoms: use of mobility aids and initial treatment

Vision-related quality of life: BCVA in the worse-seeing eye

Preference-based HRQoL: age, education, use of mobility aids, BCVA in the worse-seeing eye, number of comorbidities, number of ocular conditions, number of ocular procedures, glaucoma stage, time since diagnosis and initial treatment

Our study findings focus on the methodology used to identify the most promising predictor variables of each outcome. Previous studies solely relied on multivariable regression to identify significant variables and often conclusions from these research studies were based on significance levels. In contrast, our research study presents a novel contribution to the methodology using a combination of inferential statistics and machine learning techniques to identify the best predictor variables of an outcome. Further, the accuracy of each model was determined to provide stronger support for the conclusions. Future research can investigate how to best apply and incorporate these study findings into clinical practice guidelines for better glaucoma management. This would be a novel utilization of our research as currently very few international clinical practice guidelines incorporate evidence on PROs[194]. We also determined the accuracy of each model to provide more support for our conclusions.

The prediction models permit estimation of the patients' social support and community integration, depressive symptoms, VRQoL and preference-based HRQoL. This can be used to allow ophthalmologists to identify which patients who are at high-risk for higher depressive symptoms, lower social support and community integration, VRQoL and preference-based HRQoL.

6.4 Study Strengths and Limitations

One of the strengths of this study is the sample size (n = 250), which was large compared to previous studies assessing PROs among glaucoma patients. Another strength is that this study included patients with various levels of glaucoma severity, who had a variety of glaucoma interventions ranging from observation to surgery, and who had concurrent comorbidities. The research also benefited from low levels of missing data, so multiple imputation only needed to be performed on one variable. In addition, multiple reliable and valid PRO measurement tools were employed. A comprehensive set of PROs, using specific measurement tools as opposed to generic ones, allowed capture of precise, disease-specific results.

Most of the patients in this study had mild glaucoma as defined by Canadian practice guidelines which likely reflects the effectiveness of screening and early intervention in the community and practice in which the study was done. Patients with severe glaucoma and those living in a nursing or retirement home were under-represented in this population, which may have different outcomes if compared to a more advanced disease population.

Although our study included several types of glaucoma and other ocular conditions, results may differ if a subgroup analysis was performed, the latter which would benefit from an even larger sample size than the one examined. Also, since we conducted an exploratory analysis, some of the identified predictor variables may have associations simply by chance. Although this study was unique in utilizing a number of PROs, each is limited by their nature of being subjective and variable even among patients with similar clinical characteristics. Finally, we did not capture the patient's knowledge of glaucoma, which may present as a bias when measuring PROs.

6.5 Future Directions

This study presented proof of principle findings that provide a basis for future investigation. It would be ideal to conduct future studies intended to identify predictor variables of PROs that employ similar methodology using a combination of inferential statistics, machine learning techniques and model assessment. Previous ophthalmic studies rely on multivariable regression analysis for their analysis and interpret their results based on statistical significance. However, results should be interpreted beyond statistical significance and assess how accurately a model will perform. Machine learning techniques can provide a great contribution to ophthalmic research and practice by identifying patients at high risk for poor PROs. Further research could explore a broader range of demographic and clinical variables, and the role of other PROs among glaucoma patients.

Based on the results for the preference-based HRQoL model, where 10 predictor variables were identified, recommendations for future research would be to develop a more specific model to identify fewer predictor variables. A multicentre study that would allow input from a diverse population would be useful to confirm the association of the identified predictor variables in other settings. It would also be informative to track temporal changes in PROs, through longer

follow-up periods. Therefore, further studies with a larger diverse population stratified by disease severity and longer follow-up periods would be required for validation the latter which, however, would be limited by the challenges involved in performing long-term, multicentre studies.

6.6 Conclusion

As governments are now investing in programs aiming to increase patient input into health care decision making, studies and methodologies such as this will have continued and increased relevance. Measuring PROs is particularly useful for chronic, progressive diseases such as glaucoma as their management and treatment have a greater impact on quality of life when compared to acute and curable conditions. The importance has recently increased due to the creation of formalized programs by governments which seek direct patient input into health care decision making policies. Our research adds to the literature a novel methodology for determining predictor variables for important PROs. Our findings highlight that, in the case of glaucoma, PROs are mostly influenced by demographic characteristics, rather than clinical characteristics.

The study results support the potential of developing a clinical tool that may allow clinicians to identify patients who may benefit from additional support and resources, beyond routine clinical care and treatment. Comprehensive and targeted rehabilitative services can be developed to target the needs of these patients. Studies such as this may be useful to health care policy makers when making decisions on how to best allocate resources directed to patient-centered approaches to health care. Although, inherently subjective, patient input into their health care has become a priority for a number of countries, including Canada. As this is a relatively recent initiative, evidence to guide this process would help ensure the most cost-effective implementation of such programs. In the case of glaucoma, it would be important to stress the context, which requires research across various ophthalmic practice settings. For instance, patient's experience can be influenced by wait times, the type and location of the health care facility, relationship with the ophthalmologist and administrative staff, access to innovations in care, etc. Among our study population, the PROs were found to be high, revealing that patients were satisfied with the quality of care. Many of the patients expressed their trust in the ophthalmologist, so that they did not have to stress about their glaucoma progression. Since the patients in our study were only

recruited from one practice, our results may only be generalizable to patients of this ophthalmologist, her referral base and the setting in which she practices. Patients with severe glaucoma, as well as non-Caucasian patients, were under-represented in this study; thus, these results may not be generalizable to other populations and settings.

The predictive performance of each model is specific to our study population, and would need further validation among a diverse population to be generalizable. This would further elucidate the practical value of each model. Although we cannot be certain of the exact relationship between the predictor variables and each PRO, the methodology in this study provides a solid foundation upon which further studies can be done. This happens to coincide at a time in which patient-driven health care has become a priority for a number of provincial and international governments.

References

1. Liang, Y. B., Zhang, Y., Musch, D. C. & Congdon, N. Proposing new indicators for glaucoma healthcare service. *Eye Vis. Lond. Engl.* **4,** 6 (2017).

2. Giangiacomo, A. & Coleman, A. L. The Epidemiology of Glaucoma. in *Glaucoma* (eds. MD, F. G. & MD, R. S.) 13–21 (Springer Berlin Heidelberg, 2009). doi:10.1007/978-3-540-69475-5_2

3. Cruess, A. F., Gordon, K. D., Bellan, L., Mitchell, S. & Pezzullo, M. L. The cost of vision loss in Canada. 2. Results. *Can. J. Ophthalmol. J. Can. Ophtalmol.* **46,** 315–318 (2011).

4. Gordois, A. *et al.* An estimation of the worldwide economic and health burden of visual impairment. *Glob. Public Health* **7,** 465–481 (2012).

5. Milan, A. *Age and sex structure: Canada, provinces and territories, 2010*. (Statistics Canada, 2011).

6. Weldring, T. & Smith, S. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs) - ProQuest. *Health Serv. Insights* 61–68 (2013). doi:10.4137/HSI.S11093

7. Béchetoille, A. *et al.* Measurement of health-related quality of life with glaucoma: validation of the Glau-QoL 36-item questionnaire. *Acta Ophthalmol. (Copenh.)* **86,** 71–80 (2008).

8. Kaur, D., Gupta, A. & Singh, G. Perspectives on Quality of Life in Glaucoma. *J. Curr. Glaucoma Pract.* **6,** 9–12 (2012).

9. Quaranta, L. *et al.* Quality of Life in Glaucoma: A Review of the Literature. *Adv. Ther.* **33,** 959–981 (2016).

10. Jindal, V. Glaucoma A Multifactorial Disease and Its Multidimensional Management. *Int. J. Sci. Res. Publ.* **3,** (2013).

11. Robin, A. & Grover, D. S. Compliance and adherence in glaucoma management. *Indian J. Ophthalmol.* **59,** S93–S96 (2011).

12. Yuzawa, M., Fujita, K., Tanaka, E. & Wang, E. C. Y. Assessing quality of life in the treatment of patients with age-related macular degeneration: clinical research findings and recommendations for clinical practice. *Clin. Ophthalmol. Auckl. NZ* **7,** 1325–1332 (2013).

13. Krabbe, P. *The Measurement of Health and Health Status: Concepts, Methods and Applications from a Multidisciplinary Perspective*. (Elsevier Science Publishing Company Incorporated, 2016).

14. National Academies of Sciences, E. *et al. The Impact of Vision Loss*. (National Academies Press (US), 2016).

15. Alqudah, A., Mansberger, S. L., Gardiner, S. K. & Demirel, S. Vision-related Quality of Life in Glaucoma Suspect or Early Glaucoma Patients. *J. Glaucoma* **25,** 629–633 (2016).

16. Lim, N. C. S., Fan, C. H. J., Yong, M. K. H., Wong, E. P. Y. & Yip, L. W. Y. Assessment of Depression, Anxiety, and Quality of Life in Singaporean Patients With Glaucoma. *J. Glaucoma* **25,** 605–612 (2016).

17. Guedes, R. A. P. & Guedes, R. A. P. Quality of life and glaucoma. *Rev. Bras. Oftalmol.* **74,** 131–132 (2015).

18. Cheng, H.-C. *et al.* Patient-reported vision-related quality of life differences between superior and inferior hemifield visual field defects in primary open-angle glaucoma. *JAMA Ophthalmol.* **133,** 269–275 (2015).

19. Wilson, I. B. & Cleary, P. D. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* **273,** 59–65 (1995).

20. March 10 & 2016. FDA collaborates with academia to pursue patient-centric endpoints in glaucoma. Available at: https://www.healio.com/ophthalmology/glaucoma/news/online/%7B775cddff-dfe9-4c69-991f-e74a557fa1ab%7D/fda-collaborates-with-academia-to-pursue-patient-centric-endpoints-in-glaucoma. (Accessed: 29th July 2017)

21. Hart, P. M., Chakravarthy, U. & Stevenson, M. R. Questionnaire-based survey on the importance of quality of life measures in ophthalmic practice. *Eye Lond. Engl.* **12 (Pt 1),** 124–126 (1998).

22. Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee & Canadian Ophthalmological Society. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. *Can. J. Ophthalmol. J. Can. Ophtalmol.* **44 Suppl 1,** S7-93 (2009).

23. Caixinha, M. & Nunes, S. Machine Learning Techniques in Clinical Vision Sciences. *Curr. Eye Res.* **42,** 1–15 (2017).

24. De Moraes, C. G., Liebmann, J. M. & Levin, L. A. Detection and measurement of clinically meaningful visual field progression in clinical trials for glaucoma. *Prog. Retin. Eye Res.* doi:10.1016/j.preteyeres.2016.10.001

25. Waisbourd, M. *et al.* A prospective, longitudinal, observational cohort study examining how glaucoma affects quality of life and visually-related function over 4 years: design and methodology. *BMC Ophthalmol.* **15,** (2015).

26. Agarwal, R., Gupta, S. K., Agarwal, P., Saxena, R. & Agrawal, S. S. Current concepts in the pathophysiology of glaucoma. *Indian J. Ophthalmol.* **57,** 257–266 (2009).

27. Weinreb, R. N., Aung, T. & Medeiros, F. A. The Pathophysiology and Treatment of Glaucoma: A Review. *JAMA* **311,** 1901–1911 (2014).

28. Nucci, C. *Glaucoma: An Open Window to Neurodegeneration and Neuroprotection*. (Newnes, 2008).

29. National Eye Institute. Facts About Glaucoma. Available at: https://nei.nih.gov/health/glaucoma/glaucoma_facts. (Accessed: 16th January 2017)

30. Cohen, L. P. & Pasquale, L. R. Clinical Characteristics and Current Treatment of Glaucoma. *Cold Spring Harb. Perspect. Med.* **4,** a017236 (2014).

31. Weinreb, R. N. & Greve, E. L. *Glaucoma Diagnosis: Structure and Function*. (Kugler Publications, 2004).

32. Shetgar, A. C. & Mulimani, M. B. The Central Corneal Thickness in Normal Tension Glaucoma, Primary Open Angle Glaucoma and Ocular Hypertension. *J. Clin. Diagn. Res. JCDR* **7,** 1063–1067 (2013).

33. Parikh, R. S., Parikh, S. R., Navin, S., Arun, E. & Thomas, R. Practical approach to medical management of glaucoma. *Indian J. Ophthalmol.* **56,** 223–230 (2008).

34. Allingham, R. R. *et al. Shields textbook of glaucoma*. (Lippincott Williams & Wilkins, 2012).

35. Foster, P. J., Buhrmann, R., Quigley, H. A. & Johnson, G. J. The definition and classification of glaucoma in prevalence surveys. *Br. J. Ophthalmol.* **86,** 238–242 (2002).

36. Yanoff, M. & Duker, J. S. *Ophthalmology*. (Elsevier Health Sciences, 2009).

37. Scott Fraser & Richard Wormald. *Chapter 210 – Epidemiology of Glaucoma*. (Ophthalmology, 2011).

38. Cedrone, C., Mancino, R., Cerulli, A., Cesareo, M. & Nucci, C. Epidemiology of primary glaucoma: prevalence, incidence, and blinding effects. in *Progress in Brain Research* (ed. Carlo Nucci, L. C., Neville N.Osborne and Giacinto Bagetta) **173,** 3–14 (Elsevier, 2008).

39. Rn, W. *et al.* Primary open-angle glaucoma. *Nat. Rev. Dis. Primer* **2,** 16067–16067 (2016).

40. Hood, D. C. & Raza, A. S. On improving the use of OCT imaging for detecting glaucomatous damage. *Br. J. Ophthalmol.* **98,** ii1-ii9 (2014).

41. Tham, Y.-C. *et al.* Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. *Ophthalmology* **121,** 2081–2090 (2014).

42. Quigley, H. A. & Broman, A. T. The number of people with glaucoma worldwide in 2010 and 2020. *Br. J. Ophthalmol.* **90,** 262–267 (2006).

43. Cook, C. & Foster, P. Epidemiology of glaucoma: what's new? *Can. J. Ophthalmol.* **47,** 223–226 (2012).

44. Sommer, A. *et al.* Racial differences in the cause-specific prevalence of blindness in east Baltimore. *N. Engl. J. Med.* **325,** 1412–1417 (1991).

45. Muñoz, B. *et al.* Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. *Arch. Ophthalmol. Chic. Ill 1960* **118,** 819–825 (2000).

46. Ronnie, G., Ve, R. S., Velumuri, L., Asokan, R. & Vijaya, L. Importance of population-based studies in clinical practice. *Indian J. Ophthalmol.* **59,** S11–S18 (2011).

47. Shenken, E. The Scarborough glaucoma survey. *Can. Med. Assoc. J.* **95,** 595–602 (1966).

48. Perruccio, A. V., Badley, E. M. & Trope, G. E. Self-reported glaucoma in Canada: findings from population-based surveys, 1994–2003. *Can. J. Ophthalmol.* **42,** 219–226 (2007).

49. Harasymowycz, P. J., Papamatheakis, D. G., Fansi, A. K., Gresset, J. & Lesk, M. R. Validity of screening for glaucomatous optic nerve damage using confocal scanning laser

ophthalmoscopy (Heidelberg Retina Tomograph II) in high-risk populations: a pilot study. *Ophthalmology* **112,** 2164–2171 (2005).

50. Anraku, A. *et al.* The Toronto epidemiology glaucoma survey: a pilot study. *J. Ophthalmol.* **46,** 352–357 (2011).

51. Buys, Y. M. The need for 'made in Canada' glaucoma epidemiology data. *Can. J. Ophthalmol.* **46,** 300–302 (2011).

52. Am, E. *et al.* Screening for Glaucoma: Comparative Effectiveness. (2012).

53. Mills, R. P. Correlation of quality of life with clinical symptoms and signs at the time of glaucoma diagnosis. *Trans. Am. Ophthalmol. Soc.* **96,** 753–812 (1998).

54. Kyari, F., Nolan, W. & Gilbert, C. Ophthalmologists' practice patterns and challenges in achieving optimal management for glaucoma in Nigeria: results from a nationwide survey. (2016).

55. Schwartz, G. F. & Quigley, H. A. Adherence and Persistence with Glaucoma Therapy. *Surv. Ophthalmol.* **53,** S57–S68 (2008).

56. van Gestel, A. *et al.* The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* **24,** 1759–1769 (2010).

57. Nordmann, J.-P., Auzanneau, N., Ricard, S. & Berdeaux, G. Vision related quality of life and topical glaucoma treatment side effects. *Health Qual. Life Outcomes* **1,** 75 (2003).

58. Janz, N. K. *et al.* The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* **108,** 1954–1965 (2001).

59. Balkrishnan, R., Bond, J. B., Byerly, W. G., Camacho, F. T. & Anderson, R. T. Medication-related predictors of health-related quality of life in glaucoma patients enrolled in a medicare health maintenance organization. *Am. J. Geriatr. Pharmacother.* **1,** 75–81 (2003).

60. Guedes, R. A. P., Guedes, V. M. P., Freitas, S. M. & Chaoubah, A. Quality of life of medically versus surgically treated glaucoma patients. *J. Glaucoma* **22,** 369–373 (2013).

61. Thygesen, J. *et al.* Late-stage, primary open-angle glaucoma in Europe: social and health care maintenance costs and quality of life of patients from 4 countries. *Curr. Med. Res. Opin.* **24,** 1763–1770 (2008).

62. Varma, R., Lee, P. P., Goldberg, I. & Kotak, S. An Assessment of the Health and Economic Burdens of Glaucoma. *Am. J. Ophthalmol.* **152,** 515–522 (2011).

63. Vandenbroeck, S., De Geest, S., Zeyen, T., Stalmans, I. & Dobbels, F. Patient-reported outcomes (PRO's) in glaucoma: a systematic review. *Eye* **25,** 555–577 (2011).

64. Gautreau, S., Gould, O. N. & Forsythe, M. E. Aging and orthopedics: how a lifespan development model can inform practice and research. *Can. J. Surg.* **59,** 281–286 (2016).

65. Eye Health Council of Ontario. *Guidelines for the Care of Patients with Glaucoma*.

66. Gupta, D. *Glaucoma Diagnosis and Management*. (Lippincott Williams & Wilkins, 2005).

67. Hollands, H. *et al.* Do Findings on Routine Examination Identify Patients at Risk for Primary Open-Angle Glaucoma?: The Rational Clinical Examination Systematic Review. *JAMA* **309,** 2035–2042 (2013).

68. Heijl, A., Patella, V. & Bengtsson, B. *The Field Analyzer Primer 4th Edition: Effective Perimetry*. (Carl Zeiss Meditec Inc., 2012).

69. Khaw, P. T., Shah, P. & Elkington, A. R. Glaucoma—1: Diagnosis. *BMJ* **328,** 97–99 (2004).

70. Marsden, J., Stevens, S. & Ebri, A. How to measure distance visual acuity. *Community Eye Health* **27,** 16 (2014).

71. Wang, C.-W., Chan, C. L. W. & Chi, I. Overview of Quality of Life Research in Older People with Visual Impairment. *Adv. Aging Res.* **2014,** (2014).

72. Kotowski, J., Wollstein, G., Ishikawa, H. & Schuman, J. S. Imaging of the Optic Nerve and Retinal Nerve Fiber Layer: an Essential Part of Glaucoma Diagnosis and Monitoring. *Surv. Ophthalmol.* **59,** 458–467 (2014).

73. Deshpande, P. R., Rajan, S., Sudeepthi, B. L. & Abdul Nazir, C. P. Patient-reported outcomes: A new era in clinical research. *Perspect. Clin. Res.* **2,** 137–144 (2011).

74. Gardiner, S. K., Johnson, C. A. & Demirel, S. Factors Predicting the Rate of Functional Progression in Early and Suspected GlaucomaProgression Rate in Early and Suspected Glaucoma. *Invest. Ophthalmol. Vis. Sci.* **53,** 3598–3604 (2012).

75. Higgins, J. & Green, S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. (The Cochrane Collaboration, 2011).

76. Labiris, G., Giarmoukakis, A. & Kozobolis, V. P. Quality of Life (QoL) in Glaucoma Patients. (2011). doi:10.5772/25122

77. Rosenbaum, P. L., Livingston, M. H., Palisano, R. J., Galuppi, B. E. & Russell, D. J. Quality of life and health-related quality of life of adolescents with cerebral palsy. *Dev. Med. Child Neurol.* **49,** 516–521 (2007).

78. Parrish, R. K. *et al.* Visual function and quality of life among patients with glaucoma. *Arch. Ophthalmol. Chic. Ill 1960* **115,** 1447–1455 (1997).

79. Scholl, H. P. N., Massof, R. W. & West, S. *Ophthalmology and the Ageing Society*. (Springer Science & Business Media, 2013).

80. Buys, Y. M., Gaspo, R. & Kwok, K. Referral source, symptoms, and severity at diagnosis of ocular hypertension or open-angle glaucoma in various practices. *Can. J. Ophthalmol. J. Can. Ophtalmol.* **47,** 217–222 (2012).

81. Buys, Y. M. *et al.* Comparison of Newly Diagnosed Ocular Hypertension and Open-Angle Glaucoma: Ocular Variables, Risk Factors, and Disease Severity. *J. Ophthalmol.* **2012,** (2012).

82. Lee, B. L. & Wilson, M. R. Health-related quality of life in patients with cataract and glaucoma. *J. Glaucoma* **9,** 87–94 (2000).

83. Langelaan, M. *et al.* Impact of visual impairment on quality of life: a comparison with quality of life in the general population and with other chronic conditions. *Ophthalmic Epidemiol.* **14,** 119–126 (2007).

84. Ramrattan, R. S. *et al.* Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study. *Arch. Ophthalmol. Chic. Ill 1960* **119,** 1788–1794 (2001).

85. Wilson, M. R. *et al.* Functional status and well-being in patients with glaucoma as measured by the Medical Outcomes Study Short Form-36 questionnaire. *Ophthalmology* **105,** 2112–2116 (1998).

86. Organization, W. H. *International Classification of Functioning, Disability and Health: ICF*. (World Health Organization, 2001).

87. Brown, G. C. Vision and quality-of-life. *Trans. Am. Ophthalmol. Soc.* **97,** 473–511 (1999).

88. Berdeaux, G. H., Nordmann, J.-P., Colin, E. & Arnould, B. Vision-related quality of life in patients suffering from age-related macular degeneration. *J. Ophthalmol.* **139,** 271–279 (2005).

89. Ramulu, P. Glaucoma and Disability: Which tasks are affected, and at what stage of disease? *Curr. Opin. Ophthalmol.* **20,** 92–98 (2009).

90. Blane, A. Through the Looking Glass: A Review of the Literature Investigating the Impact of Glaucoma on Crash Risk, Driving Performance, and Driver Self-Regulation in Older Drivers. *J. Glaucoma* **25,** 113–121 (2016).

91. Altangerel, U., Spaeth, G. L. & Rhee, D. J. Visual function, disability, and psychological impact of glaucoma. *Curr. Opin. Ophthalmol.* **14,** 100–105 (2003).

92. Mabuchi, F. *et al.* High prevalence of anxiety and depression in patients with primary open-angle glaucoma. *J. Glaucoma* **17,** 552–557 (2008).

93. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations | SpringerLink. Available at: https://link.springer.com/article/10.1007/s11136-011-0054-x. (Accessed: 14th July 2017)

94. Vandenbroeck, S., De Geest, S., Zeyen, T., Stalmans, I. & Dobbels, F. Patient-reported outcomes (PRO's) in glaucoma: a systematic review. *Eye* **25,** 555–577 (2011).

95. Browne, C., Brazier, J., Carlton, J., Alavi, Y. & Jofre-Bonet, M. Estimating quality-adjusted life years from patient-reported visual functioning. *Eye* **26,** 1295–1301 (2012).

96. Gupta, V. *et al.* Utility values among glaucoma patients: an impact on the quality of life. *Br. J. Ophthalmol.* **89,** 1241–1244 (2005).

97. Che Hamzah, J., Burr, J. M., Ramsay, C. R., Azuara-Blanco, A. & Prior, M. Choosing appropriate patient-reported outcomes instrument for glaucoma research: a systematic review of vision instruments. *Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil.* **20,** 1141–1158 (2011).

98. Shaarawy, T., Sherwood, M. B. & Crowston, J. G. *Glaucoma: Medical diagnosis & therapy*. (Elsevier Health Sciences, 2009).

99. Sherwood, M. B. *et al.* Glaucoma's impact on quality of life and its relation to clinical indicators. A pilot study. *Ophthalmology* **105,** 561–566 (1998).

100. Mangione, C. M. *et al.* Psychometric Properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch. Ophthalmol.* **116,** 1496–1504 (1998).

101. Hirsh, A. T., Braden, A. L., Craggs, J. G. & Jensen, M. P. Psychometric properties of the community integration questionnaire in a heterogeneous sample of adults with physical disability. *Arch. Phys. Med. Rehabil.* **92,** 1602–1610 (2011).

102. Visual Impairment and Disability in Older Adults. : Optometry and Vision Science. *LWW* Available at: http://journals.lww.com/optvissci/Fulltext/1994/12000/Visual_Impairment_and_Disability_in_Older_Adults_.5.aspx. (Accessed: 8th July 2017)

103. Rapport, L. J., Bryer, R. C. & Hanks, R. A. Driving and Community Integration After Traumatic Brain Injury. *Arch. Phys. Med. Rehabil.* **89,** 922–930 (2008).

104. Reblin, M. & Uchino, B. N. Social and Emotional Support and its Implication for Health. *Curr. Opin. Psychiatry* **21,** 201–205 (2008).

105. Kratz, A. L., Chadd, E., Jensen, M. P., Kehn, M. & Kroll, T. An examination of the psychometric properties of the community integration questionnaire (CIQ) in spinal cord injury. *J. Spinal Cord Med.* **38,** 446–455 (2015).

106. Sander, A. M. *et al.* The community integration questionnaire revisited: An assessment of factor structure and validity. *Arch. Phys. Med. Rehabil.* **80,** 1303–1308 (1999).

107. Willer, B., Rosenthal, M., Kreutzer, J. ., Gordan, W. . & Rempel, R. Assessment of community integration following rehabilitation... : The Journal of Head Trauma Rehabilitation. *J. Head Trauma Rehabil.* 75–87 (1993).

108. Willer, B., Ottenbacher, K. J. & Coad, M. L. The community integration questionnaire. A comparative examination. *Am. J. Phys. Med. Rehabil.* **73,** 103–111 (1994).

109. Singh, U. & Sharma, V. Validity and reliability of community integration questionnaire in elderly. *Int. J. Health Rehabil. Sci. IJHRS* **4,** 1–9 (2015).

110. Garcia, G. A. *et al.* Profound vision loss impairs psychological well-being in young and middle-aged individuals. *Clinical Ophthalmology* (2017). Available at: https://www.dovepress.com/profound-vision-loss-impairs-psychological-well-being-in-young-and-mid-peer-reviewed-article-OPTH. (Accessed: 17th March 2017)

111. Tastan, S., Iyigun, E., Bayer, A. & Acikel, C. Anxiety, depression, and quality of life in Turkish patients with glaucoma. *Psychol. Rep.* **106,** 343–357 (2010).

112. Kroenke, K. *et al.* Patient Health Questionnaire Anxiety and Depression Scale: Initial Validation in Three Clinical Trials. *Psychosom. Med.* **78,** 716–727 (2016).

113. Skalicky, S. & Goldberg, I. Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision, and the Glaucoma Quality of Life-15. *J. Glaucoma* **17,** 546–551 (2008).

114. Eack, S. M., Greeno, C. G. & Lee, B.-J. Limitations of the Patient Health Questionnaire in Identifying Anxiety and Depression: Many Cases Are Undetected. *Res. Soc. Work Pract.* **16,** 625–631 (2006).

115. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16,** 606–613 (2001).

116. Hyman, L. G., Komaroff, E., Heijl, A., Bengtsson, B. & Leske, M. C. Treatment and Vision-Related Quality of Life in the Early Manifest Glaucoma Trial. *Ophthalmology* **112,** 1505–1513 (2005).

117. Dr, G. *et al.* Using focus groups to develop a culturally sensitive methodology for epidemiological surveys in a Latino population: findings from the Los Angeles Latino Eye Study (LALES). *Ethn. Dis.* **12,** 259–266 (2001).

118. Hirneiss, C. The impact of a better-seeing eye and a worse-seeing eye on vision-related quality of life. *Clin. Ophthalmol. Auckl. NZ* **8,** 1703–1709 (2014).

119. Jampel, H. D. Glaucoma patients' assessment of their visual function and quality of life. *Trans. Am. Ophthalmol. Soc.* **99,** 301–317 (2001).

120. Shaarawy, T. M., Sherwood, M. B., Hitchings, R. A. & Crowston, J. G. *Glaucoma E-Book*. (Elsevier Health Sciences, 2014).

121. Spratt, A., Kotecha, A. & Viswanathan, A. Quality of Life in Glaucoma. **2,** 39–45 (2008).

122. Bass, E. B. *et al.* Preference values for visual states in patients planning to undergo cataract surgery. *Med. Decis. Mak. Int. J. Soc. Med. Decis. Mak.* **17,** 324–330 (1997).

123. Brown, M. M., Brown, G. C., Sharma, S. & Shah, G. Utility values and diabetic retinopathy. *Am. J. Ophthalmol.* **128,** 324–330 (1999).

124. Saw, S., Gazzard, G., Eong, K. A., Oen, F. & Seah, S. Utility Values in Singapore Chinese Adults With Primary Open-angle and Primary Angle-closure Glaucoma. *J. Glaucoma* **14,** 455–462 (2005).

125. Aspinall, P. A. *et al.* Evaluation of Quality of Life and Priorities of Patients with Glaucoma. *Invest. Ophthalmol. Vis. Sci.* **49,** 1907–1915 (2008).

126. Ferrans, C. E., Zerwic, J. J., Wilbur, J. E. & Larson, J. L. Conceptual model of health-related quality of life. *J. Nurs. Scholarsh. Off. Publ. Sigma Theta Tau Int. Honor Soc. Nurs.* **37,** 336–342 (2005).

127. Heslin, K. C. *et al.* Clinical correlates of health-related quality of life among opioid-dependent patients. *Qual. Life Res.* **20,** 1205–1213 (2011).

128. Hastie, T., Tibshirani, R. & Friedman, J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. (Springer, 2008).

129. Bow-Thomas, C. C., Velligan, D. I., Miller, A. L. & Olsen, J. Predicting quality of life from symptomatology in schizophrenia at exacerbation and stabilization. *Psychiatry Res.* **86,** 131–142 (1999).

130. Benedict, R. H. B. *et al.* Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J. Neurol. Sci.* **231,** 29–34 (2005).

131. Kowalchuk, D. A., Harner, C. D., Fu, F. H. & Irrgang, J. J. Prediction of patient-reported outcome after single-bundle anterior cruciate ligament reconstruction. *Arthrosc. J. Arthrosc. Relat. Surg. Off. Publ. Arthrosc. Assoc. N. Am. Int. Arthrosc. Assoc.* **25,** 457–463 (2009).

132. Horng, Y.-S. *et al.* Predicting health-related quality of life in patients with low back pain. *Spine* **30,** 551–555 (2005).

133. Hatzmann, J., Maurice-Stam, H., Heymans, H. S. & Grootenhuis, M. A. A predictive model of Health Related Quality of life of parents of chronically ill children: the importance of care-dependency of their child and their support system. *Health Qual. Life Outcomes* **7,** 72 (2009).

134. Khedmat, H. *et al.* A logistic regression model for predicting health-related quality of life in kidney transplant recipients. *Transplant. Proc.* **39,** 917–922 (2007).

135. Wang, J., Sereika, S. M., Styn, M. A. & Burke, L. E. Factors associated with health-related quality of life among overweight or obese adults. *J. Clin. Nurs.* **22,** 2172–2182 (2013).

136. Heslin, K. C. *et al.* Clinical correlates of health-related quality of life among opioid-dependent patients. *Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil.* **20,** 1205–1213 (2011).

137. Hirasawa, H., Murata, H., Mayama, C., Araie, M. & Asaoka, R. Evaluation of various machine learning methods to predict vision-related quality of life from visual field data and visual acuity in patients with glaucoma. *Br. J. Ophthalmol.* **98,** 1230–1235 (2014).

138. Sharma, S. *et al.* Converting visual acuity to utilities. *Can. J. Ophthalmol. J. Can. Ophtalmol.* **35,** 267–272 (2000).

139. Soper, D. A-priori Sample Size for Multiple Regression References - Free Statistics Calculators. *Free Statistics Calculator* (2017). Available at: http://www.danielsoper.com/statcalc/references.aspx?id=1. (Accessed: 15th March 2017)

140. Rein, D. B., Wirth, K. E., Johnson, C. A. & Lee, P. P. Estimating quality-adjusted life year losses associated with visual field deficits using methodological approaches. *Ophthalmic Epidemiol.* **14,** 258–264 (2007).

141. Bhargava, J. S., Bhan-Bhargava, A., Foss, A. J. E. & King, A. J. Views of glaucoma patients on provision of follow-up care; an assessment of patient preferences by conjoint analysis. *Br. J. Ophthalmol.* **92,** 1601–1605 (2008).

142. PRIME PubMed | Utility assessment among patients of primary angle closure/glaucoma in China: a preliminary stud. Available at: https://www.unboundmedicine.com/medline/citation/19208679/Utility_assessment_among_patients_of_primary_angle_closure/glaucoma_in_China:_a_preliminary_study_. (Accessed: 14th March 2017)

143. Tuulonen, A. Economic considerations of the diagnosis and management for... : Current Opinion in Ophthalmology. *Curr. Opin. Ophthalmol.* (2011). doi:10.1097/ICU.0b013e3283437bf0

144. Alavi, Y. *et al.* Developing an Algorithm to Convert Routine Measures of Vision into Utility Values for Glaucoma. *Ophthalmic Epidemiol.* **18,** 233–243 (2011).

145. Gupta, V. *et al.* Effect of Glaucoma on the Quality of Life of Young Patients. *Invest. Ophthalmol. Vis. Sci.* **52,** 8433–8437 (2011).

146. Kishimoto, F., Naito, T., Hasebe, S. & Ohtsuki, H. Time Trade-off Utility Analysis for Surgical Intervention in Comitant Strabismus, Glaucoma, and Cataract. *Acta Medica Okayama* (2012). Available at: http://ousar.lib.okayama-u.ac.jp/48558. (Accessed: 14th March 2017)

147. Bozzani, F. M., Alavi, Y., Jofre-Bonet, M. & Kuper, H. A comparison of the sensitivity of EQ-5D, SF-6D and TTO utility values to changes in vision and perceived visual function in patients with primary open-angle glaucoma. *BMC Ophthalmol.* **12,** 43 (2012).

148. Attema, A. E., Edelaar-Peeters, Y., Versteegh, M. M. & Stolk, E. A. Time trade-off: one methodology, different methods. *Eur. J. Health Econ.* **14,** 53–64 (2013).

149. Gothwal, V. K. *et al.* Is Utility-Based Quality of Life in Adults Affected by Glaucoma?Utility-Based Quality of Life in Glaucoma. *Invest. Ophthalmol. Vis. Sci.* **55,** 1361–1369 (2014).

150. Paletta Guedes, R. A., Paletta Guedes, V. M., Freitas, S. M. & Chaoubah, A. Utility values for glaucoma in Brazil and their correlation with visual function. *Clin. Ophthalmol. Auckl. NZ* **8,** 529–535 (2014).

151. Zhang, S. *et al.* Utility Analysis of Vision-related Quality of Life in Patients With Glaucoma and Different Perceptions from Ophthalmologists. *J. Glaucoma* **24,** 508–514 (2015).

152. Paletta Guedes, R. A., Paletta Guedes, V. M., Freitas, S. M. & Chaoubah, A. Does the type of treatment have an influence on utility values in a glaucoma population? *Clin. Ophthalmol. Auckl. NZ* **9,** 1645–1650 (2015).

153. Ma, Y. *et al.* Cost-Utility Analyses of Cataract Surgery in Advanced Age-Related Macular Degeneration. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **93,** 165–172 (2016).

154. DHS Century Month Codes | Tools for Demographic Estimation. Available at: http://demographicestimation.iussp.org/content/dhs-century-month-codes. (Accessed: 3rd April 2017)

155. Cusick, C. P., Gerhart, K. A. & Mellick, D. C. Participant-proxy reliability in traumatic brain injury outcome research. *J. Head Trauma Rehabil.* **15,** 739–749 (2000).

156. Arrieta, J. *et al.* Validity and Utility of the Patient Health Questionnaire (PHQ)-2 and PHQ-9 for Screening and Diagnosis of Depression in Rural Chiapas, Mexico: A Cross-Sectional Study. *J. Clin. Psychol.* (2017). doi:10.1002/jclp.22390

157. Mangione, C. M. *et al.* Development of the 25-list-item National Eye Institute Visual Function Questionnaire. *Arch. Ophthalmol.* **119,** 1050–1058 (2001).

158. Revicki, D. A., Rentz, A. M., Harnam, N., Thomas, V. S. & Lanzetta, P. Reliability and Validity of the National Eye Institute Visual Function Questionnaire-25 in Patients with Age-Related Macular Degeneration. *Invest. Ophthalmol. Vis. Sci.* **51,** 712–717 (2010).

159. Brown, G. C., Brown, M. M., Sharma, S., Beauchamp, G. & Hollands, H. The reproducibility of ophthalmic utility values. *Trans. Am. Ophthalmol. Soc.* **99,** 199–204 (2001).

160. Hollands, H. *et al.* Reliability of the time trade-off technique of utility assessment in patients with retinal disease. *Can. J. Ophthalmol. J. Can. Ophtalmol.* **36,** 202–209 (2001).

161. Enders, C. K. *Applied Missing Data Analysis*. (Guilford Press, 2010).

162. Ryder, A. B. *et al.* The Advantage of Imputation of Missing Income Data to Evaluate the Association Between Income and Self-Reported Health Status (SRH) in a Mexican American Cohort Study. *J. Immigr. Minor. Health Cent. Minor. Public Health* **13,** 1099–1109 (2011).

163. Rubin, D. B. *Multiple Imputation for Nonresponse in Surveys*. (John Wiley & Sons, 2004).

164. Vach, W. *Regression Models as a Tool in Medical Research*. (CRC Press, 2012).

165. thebmj. 11. Correlation and regression | The BMJ. *The BMJ Research* Available at: http://www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/11-correlation-and-regression. (Accessed: 23rd August 2017)

166. Institute for Digital Research and Education. Regression with Stata Chapter 2 - Regression Diagnostics. *IDRE Stats* Available at: https://stats.idre.ucla.edu/stata/webbooks/reg/chapter2/stata-webbooksregressionwith-statachapter-2-regression-diagnostics/. (Accessed: 9th June 2017)

167. Bernhardt, V. *Using Data to Improve Student Learning in School Districts*. (Routledge, 2013).

168. Vittinghoff, E., Glidden, D. V., Shiboski, S. C. & McCulloch, C. E. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. (Springer Science & Business Media, 2011).

169. Bursac, Z., Gauss, C. H., Williams, D. K. & Hosmer, D. W. Purposeful selection of variables in logistic regression. *Source Code Biol. Med.* **3,** 17 (2008).

170. Fischetti, T. *Data Analysis with R*. (Packt Publishing Ltd, 2015).

171. Beal, D. J. *SAS® Code to Select the Best Multiple Linear Regression Model for Multivariate Data Using Information Criteria*.

172. Venables, W. . & Ripley, B. . *Modern Applied Statistics with S*. (Springer, 2002).

173. Loh, W.-Y. Classification and regression trees. *Wiley Interdiscip. Rev. Data Min. Knowl. Discov.* **1,** 14–23 (2011).

174. De'ath, G. & Fabricius, K. E. Classification and Regression Trees: A Powerful yet Simple Technique for Ecological Data Analysis. *Ecology* **81,** 3178–3192 (2000).

175. Ravi, K. B. & Serra, J. Cost-complexity pruning of random forests. *ArXiv170305430 Cs Stat* (2017).

176. Kohavi, R. A Study of Cross-validation and Bootstrap for Accuracy Estimation and Model Selection. *Proc. 14th Int. Jt. Conf. Artif. Intell. - Vol. 2* 1137–1143 (1995).

177. James, G., Witten, D., Hastie, T. & Tibshirani, R. Resampling Methods. in *An Introduction to Statistical Learning* 175–201 (Springer New York, 2013). doi:10.1007/978-1-4614-7138-7_5

178. Chai, T. & Draxler, R. R. Root mean square error (RMSE) or mean absolute error (MAE)? - Arguments against avoiding RMSE in the literature. *Geosci. Model Dev.* **7,** 1247–1250 (2014).

179. Carter, R. E. A Standard Error: Distinguishing Standard Deviation From Standard Error. *Diabetes* **62,** e15–e15 (2013).

180. SONG, Y. & LU, Y. Decision tree methods: applications for classification and prediction. *Shanghai Arch. Psychiatry* **27,** 130–135 (2015).

181. What's the Best R-Squared for Logistic Regression | Statistical Horizons. Available at: https://statisticalhorizons.com/r2logistic. (Accessed: 21st June 2017)

182. Wilson, M. R. *et al.* Depression in patients with glaucoma as measured by self-report surveys. *Ophthalmology* **109,** 1018–1022 (2002).

183. McIlraith, I., Strasfeld, M., Colev, G. & Hutnik, C. M. L. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J. Glaucoma* **15,** 124–130 (2006).

184. Toprak, A., Ester, E., Guler, C., Baser, F. & Mayali, H. Cross-validation of the Turkish Version of the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ 25): Ophthalmic Epidemiology: Vol 12, No 4. **12,** 259–269

185. Karadeniz Ugurlu, S., Kocakaya Altundal, A. E. & Altin Ekin, M. Comparison of vision-related quality of life in primary open-angle glaucoma and dry-type age-related macular degeneration. *Eye* **31,** 395–405 (2017).

186. Pujol Carreras, O. *et al.* Quality of life in glaucoma patients and normal subjects related to the severity of damage in each eye. *Arch. Soc. Espanola Oftalmol.* **1,** (2017).

187. Cahill, M. T., Banks, A. D., Stinnett, S. S. & Toth, C. A. Vision-related quality of life in patients with bilateral severe age-related macular degeneration. *Ophthalmology* **112,** 152–158 (2005).

188. Peters, D., Heijl, A., Brenner, L. & Bengtsson, B. Visual impairment and vision-related quality of life in the Early Manifest Glaucoma Trial after 20 years of follow-up. *Acta Ophthalmol. (Copenh.)* **93,** 745–752 (2015).

189. Identifying Areas of the Visual Field Important for Quality of Life in Patients with Glaucoma. Available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0058695. (Accessed: 28th June 2017)

190. Takahashi, G., Otori, Y., Urashima, M., Kuwayama, Y. & Quality of Life Improvement Committee. Evaluation of Quality of Life in Japanese Glaucoma Patients and its Relationship With Visual Function. *J. Glaucoma* **25,** e150-156 (2016).

191. Sun, Y. *et al.* The Impact of Visual Field Clusters on Performance-based Measures and Vision-Related Quality of Life in Patients With Glaucoma. *Am. J. Ophthalmol.* **163,** 45–52 (2016).

192. Jampel, H. D. *et al.* Glaucoma patients' assessment of their visual function and quality of life. *J. Glaucoma* **11,** 154–163 (2002).

193. Kobelt, G. *et al.* Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol. Scand.* **84,** 363–371 (2006).

194. Armstrong, J. J., Goldfarb, A. M., Instrum, R. S. & MacDermid, J. C. Improvement evident but still necessary in clinical practice guideline quality: a systematic review. *J. Clin. Epidemiol.* **81,** 13–21 (2017).

Appendices

Appendix A. Research Ethics Board approval letter

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Monali Malvankar
Department & Institution: Schulich School of Medicine and Dentistry\Ophthalmology,Western University

Review Type: Expedited
HSREB File Number: 104569
Study Title: Health Related Quality of Life (HRQoL) for Patients Suffering from Glaucoma and Diabetic Retinopathy

HSREB Amendment Approval Date: February 24, 2016
HSREB Expiry Date: December 11, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Questionnaire-Received Jan 27, 2016	2016/01/15
Revised Letter of Information & Consent		2016/01/19

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Basile ✓ Katelyn Harris ___ Nicole Kaniki ___ Grace Kelly ___ Vikki Tran ___

This is an official document. Please return the original in your files

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/ethics

Appendix B: Sample size calculation formulas

1. Beta function:

$$B(x,y) = \int_0^x t^{x-1}(1-t)^{y-1}dt$$

where *B* is the normalization constant

x and y are real numbers

2. Cohen's f^2 effect size for an F-test:

$$f^2 = \frac{R^2}{1-R^2}$$

where R^2 is the squared multiple correlation

3. Error function:

$$erf(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}dt$$

where $\frac{2}{\sqrt{\pi}}$ is the normalization factor, defined as the probability density function

4. F-distribution cumulative distribution function:

$$F(x; d_1, d_2) = I_{\frac{d_1 x}{d_1 x + d_2}}(\frac{d_1}{2}, \frac{d_2}{2})$$

where d_1 and d_2 are the degrees of freedom

I is the regularized lower incomplete beta function ($\frac{B(x;a,b)}{B(a,b)}$)

5. Non-central F-distribution cumulative distribution function:

$$F(x|d_1, d_2, \lambda) = \sum_{j=0}^{\infty}(\frac{(\frac{1}{2}\lambda)^j}{j!})e^{-\frac{\lambda}{2}}\ I(\frac{d_1 F}{d_2 + d_1 F}|\frac{d_1}{2} + j, \frac{d_2}{2})$$

where d_1 and d_2 are the numerator and denominator degrees of freedom

λ is the non-central parameter

F is the Fisher F-value

I is the regularized lower incomplete beta function ($\frac{B(x;a,b)}{B(a,b)}$)

6. Non-central F-distribution parameter:

$$\lambda = f^2 n$$

where f^2 is the effect size

n is the sample size

7. Normal distribution cumulative distribution function:

$$F(x;\mu,\sigma^2) = \frac{1}{2}[1 + erf\ (\frac{x-\mu}{\sigma\sqrt{2}})]$$

where μ is the mean

σ is the standard deviation

erf is the error function

Appendix C. Community Integration Questionnaire (CIQ)

1. Who usually does the shopping for groceries or other necessities in your household?	o Yourself alone o Yourself and someone else o Someone else
2. Who usually prepares meals in your household?	o Yourself alone o Yourself and someone else o Someone else
3. In your home who usually does the everyday housework?	o Yourself alone o Yourself and someone else o Someone else o Not applicable
4. Who usually cares for the children in your home?	o Yourself alone o Yourself and someone else o Someone else o Not applicable
5. Who usually plans social arrangements such as get-togethers with family and friends?	o Yourself alone o Yourself and someone else o Someone else
6. Who usually looks after your personal finances, such as banking or paying bills	o Yourself alone o Yourself and someone else o Someone else
7. Approximately how many times a month do you usually participate in shopping *outside* your home?	o Never o 1-4 times o 5 or more
8. Approximately how many times a month do you usually participate in leisure activities such as movies, sports, restaurants etc.	o Never o 1-4 times o 5 or more
9. Approximately how many times a month do you usually visit your friends or relatives?	o Never o 1-4 times o 5 or more
10. When you participate in leisure activities do you usually do this alone or with others?	o Mostly alone o Mostly with friends o Mostly with family members o With a combination of family and friends
11. Do you have a best friend with whom you confide?	o Yes o No
12. How often do you travel outside the home?	o Almost every day o Almost every week o Seldom/never (less than once per week)

13. Please choose the answer that best corresponds to your current (during the past month) work situation:	o Full-time (more than 20 hours/week) o Part-time (less than or equal to 20 hours/week) o Not working, but actively looking for work o Not working, not looking for work o Not applicable (retired, disability)
14. Please choose the answer that best corresponds to your current (during the past month) school or training program situation:	o Full-time o Part-time o Not attending school, or training program o Not applicable (retired, disability)
15. In the past month, how often did you engage in volunteer activities	o Never o 1-4 times o 5 or more

**(adapted from: Dijkers, M. (2000). The Community Integration Questionnaire. The Center for Outcome Measurement in Brain Injury. http://www.tbims.org/combi/ciq)*

Appendix D. Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several Days	More than half the days	Nearly Every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself- or that you are a failure or have let yourself or family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

Add Columns _____ + _____ + _____

Total _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of the things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

** Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute*

Appendix E. National Eye Institute Visual Function Questionnaire – 25 (NEI VFQ-25)

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is: (Circle One)

Excellent..... 1
Very Good..... 2
Good..... 3
Fair..... 4
Poor..... 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind? (Circle One)

Excellent..... 1
Good..... 2
Fair..... 3
Poor..... 4
Very Poor..... 5
Completely Blind..... 6

3. How much of the time do you worry about your eyesight? (Circle One)

None of the time..... 1
A little of the time..... 2
Some of the time..... 3
Most of the time..... 4
All of the time?..... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is: (Circle One)

None..... 1
Mild..... 2
Moderate..... 3
Severe, or..... 4
Very severe?..... 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have: (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say: (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

8. How much difficulty do you have reading street signs or the names of stores?(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3

Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events? (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

15. Are you currently driving, at least once in a while? (Circle One)

Yes..... 1 Skip To Q 15c
No 2

15a. IF NO: Have you never driven a car or have you given up driving? (Circle One)

Never drove..... 1 Skip To Part 3, Q 17

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons? (Circle One)

Mainly eyesight..... 1 Skip To Part 3, Q 17
Mainly other reasons ..... 2 Skip To Part 3, Q 17
Both eyesight and other reasons .... 3 Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have: (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have: (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have: (Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time. (Circle One On Each Line)

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
17	Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18	Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19	How much does pain or	1	2	3	4	5

	discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing?					

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure. (Circle One On Each Line)

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
20	I stay home most of the time because of my eyesight.	1	2	3	4	5
21	I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22	I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23	Because of my eyesight, I have to rely too much on what other people tell me	1	2	3	4	5
24	I need a lot of help from others because of my eyesight.	1	2	3	4	5
25	I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix F. Time Trade-Off (TTO)

How many years do you expect to live? _____years

Suppose there was a new technology that could restore your eyesight to perfectly normal in both eyes. The technology always works but decreases the length of time you live.

What is the maximum number of years, if any, that you would be **willing to give up** if you could receive this technology and have **perfect vision** for your remaining years?

_____years

Curriculum Vitae

Name:	Lavanya Uruthiramoorthy
Post-secondary Education and Degrees:	Western University London, Ontario, Canada 2015 – 2017 MSc. Epidemiology & Biostatistics Humber Institute of Technology and Advanced Learning Toronto, Ontario, Canada 2012 – 2013 Postgraduate Certificate, Clinical Research University of Waterloo Waterloo, Ontario, Canada 2008 – 2012 BSc. (Honours)
Honours and Awards:	Department of Epidemiology & Biostatistics 2015 – 2017 Western Graduate Research Scholarship

Conference Presentations:

Uruthiramoorthy L., Lizotte, D.J., Malvankar M.S., & Hutnik C.M.L. Impact of first line treatment on quality of life among glaucoma and glaucoma suspect patients. *Canadian Ophthalmological Society Annual Meeting and Exhibition, Palais des Congres, Montreal, Quebec. June 17, 2017.* (Poster presentation)

Uruthiramoorthy L., Lizotte, D.J., Malvankar M.S., Speechley K.N., & Hutnik C.M.L. Predicting important patient domains for glaucoma management. *Canadian Society for Epidemiology and Biostatistics Biennial Conference, Banff Centre, Banff, Alberta. May 31, 2017.* (Oral presentation)

Uruthiramoorthy L., Lizotte, D.J., Malvankar M.S., & Hutnik C.M.L. Quality of life among glaucoma patients: Key clinical and demographic variable. *Annual Meeting of the Association for Research in Vision and Ophthalmology, Baltimore Convention Center, Baltimore, Maryland. May 9, 2017*. (Poster presentation)

Uruthiramoorthy L., Lizotte, D.J., Malvankar M.S., & Hutnik C.M.L. Health-Related Quality of Life in Patients with Glaucoma and Glaucoma Suspects: Cross-sectional Study. *Ophthalmology Research Day, Best Western Lamplighter, London ON. November 4, 2016.* (Oral presentation)

Uruthiramoorthy L., Lizotte, D.J., Malvankar M.S., & Hutnik C.M.L. Health-Related Quality of Life of Patients with Glaucom*a*. *Ophthalmology Research Day, Best Western Lamplighter, London. November 6, 2015.* (Oral presentation)