6-30-2015 12:00 AM

The Effectiveness of Teleglaucoma versus In-patient Examination. Assessment: Systematic Review, Meta-Analysis, and Cost-Effectiveness Analysis

Sera-Melisa Thomas, *The University of Western Ontario*

Supervisor: Dr. Monali Malvankar-Mehta, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

THE EFFECTIVENESS OF TELEGLAUCOMA VERSUS IN-PATIENT EXAMINATION

ASSESSMENT: SYSTEMATIC REVIEW, META-ANALYSIS AND COST-EFFECTIVENESS ANALYSIS

(Thesis format: Integrated Article)

by

Sera-Melisa Thomas

Graduate Program in Epidemiology & Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Masters of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

Teleglaucoma is a screening device that remotely detects glaucoma cases at earlier stages using electronically-transferred stereoscopic digital imaging. Thus, patient wait and travel times are reduced, as well as, patient load in ophthalmic clinics. The purpose is to synthesize literature to evaluate teleglaucoma: its diagnostic accuracy, the healthcare system benefits, and its cost-effectiveness. A systematic review was conducted with published and unpublished studies. A meta-analysis was conducted to provide estimates of diagnostic accuracy, diagnostic odds ratio, and the relative percentage of glaucoma cases detected. Using Markov Modelling, a cost-effectiveness analysis was conducted. Of 11237 studies reviewed, 45 were included. Teleglaucoma was more specific and less sensitive than in-person examination. The pooled estimates of sensitivity was 0.832 [95% CI 0.770, 0.881] and specificity was 0.790 [95% CI 0.668, 0.876]. The ICER calculated for teleglaucoma was $27,460/QALY. In conclusion, teleglaucoma was found to be more cost-effective than in-person examination in rural areas.

Keywords

Teleglaucoma, tele-ophthalmology, screening, digital photography, diagnostic accuracy, glaucoma, ophthalmology, systematic review, meta-analysis, cost-effectiveness analysis

Co-Authorship Statement

Chapter 3: The effectiveness of teleglaucoma versus in-person examination (Systematic Review and Meta-Analysis)

Co-authorship Thomas S, Jeyaraman M, Hodge W, Hutnik C, Costella J, Malvankar-Mehta M.

Thomas S and Malvankar-Mehta M framed the study concept and study design. Thomas S, Jeyaraman M, and Costella J conducted the literature search and article retrieval. Thomas S performed the data extraction and conducted the data analysis. Results and conclusions were generated by Thomas S with feedback from Hodge W, Hutnik C, and Malvankar-Mehta M. Thomas S wrote the manuscript with revisions and content feedback from Hodge W, Hutnik C, Costella J, and Malvankar-Mehta M.

Dedication

I would like to dedicate this thesis to my Brother, Sister, Mother and Best Friend for their unconditional love and inspiration through this journey.

As my mom always says,

“For only by earnest endeavor, the highest we shall attain”

- Sera

Acknowledgments

Firstly, I would like to acknowledge the Department of Epidemiology & Biostatistics at Western University. It is an honour to be part of a successful academic environment that fosters not only educational learning, but academic scholarship, practical hands-on experiences, and professional development. The faculty and administrative staff have shown me continuous support throughout my graduate school experience and I am truly grateful. Specifically, I would like to express my sincerest gratitude and appreciation to Dr. Greta Bauer for her invaluable mentorship that has been instrumental in my personal and professional growth.

My research would not be possible or successful without the assistance of my advisory committee members Drs. Cindy Hutnik and William Hodge. I greatly appreciate their availability and the countless hours they have put into advising me with my research projects. My learning experience during my time at the *Ivey Eye Institute*, though only two years, was bountiful. I am most grateful for the many opportunities and resources, Drs. Hodge and Hutnik have provided me with. They are not only great advisors, but wonderful people and I am eternally grateful for their continuous dedication to my development as a researcher.

I would like to thank the team at the *Ivey Eye Institute*. Richie, Eddie, Vlad, Nancy and Pan, we have shared research advice and many memorable moments. A special thank you to my MSc cohort, I have never experienced such teamwork and comradery. Especially Vinusha who has always been there for me.

Finally, I would like to thank my supervisor Dr. Monali Malvankar. She has motivated me and has helped me excel throughout this graduate school experience. Thank you Dr. Monali for your continuous support!

Table of Contents

List of Tables

Table 4.7: Accumulate Rewards, Costs, and Probabilities after 30 years

List of Figures

List of Appendices

List of Abbreviations

AAO	American Academy of Ophthalmology
ARVO	Association for Research in Vision and Ophthalmology
CAN	Canadian Currency (Dollars)
CCT	Central Corneal Thickness
CDR	Cup-to-Disc Ratio
CEA	Cost-Effectiveness Analysis
CNIB	Canadian National Institute for the Blind
COS	Canadian Ophthalmology Society
DOR	Diagnostic Odds Ratio
DSA	Deterministic Sensitivity Analysis
EUR	European Currency (Euros)
FDT	Frequency Doubling Technology
GHT	Glaucoma Hemifeld Test
GRADE	Grading of Recommendations, Assessments, Development, and Evaluation
HFA	Humphrey Visual Field Analyzer
HRQoL	Health-Related Quality of Life
HRT	Heidelberg Retinal Tomography
HSROC	Hierarchical Summary Receiver-Operator Curve

ICER	Incremental Cost-Effectiveness Ratio
IOP	Intraocular Pressure
ISNT	Inferior, Superior, Nasal, and Temporal
LR	Likelihood Ratio
NFL	Nerve Fiber Layer
OAG	Open-Angle Glaucoma
OCT	Optical Coherence Tomography
PERL	Pupil Equal and Reactive to Light
QALY	Quality Adjusted Life Years
RAPD	Relative Afferent Pupillary Defect
RCT	Randomized Control Trial
SDI	Secure Diagnostic Imaging
US	United States Currency (Dollars)
VCDR	Vertical Cup to Disk Ratio
VF	Visual Field
WTP	Willingness-to-Pay

Chapter 1 Introduction

1 Introduction

The burden of vision loss on the Canadian economy is $15.8 billion per year in which 55% is allocated to direct health care costs.[1] Sixty-five per cent of adults with partial or full vision loss are unemployed, which translates to $4.06 CAN billion annually of lost earnings.[1] In the United States, vision loss costs over $35 billion for direct costs and loss of productivity.[2] Glaucoma is the major eye disease leading to irreversible vision loss. The economic burden of glaucoma alone on the American economy is $2.9 billion.[2]

Glaucoma tends to be detected at later stages of the disease when glaucoma has advanced into vision impairment due to peripheral visual field loss. Patients have "tunnel vision," but may have perfect central vision. As a result, patients may not notice visual field loss until advance stages of disease. Detection of glaucoma at earlier stages is important for treatment and to prevent the progression of disease.[3]

Teleglaucoma is a screening device that can help detect glaucoma patients at earlier stages by remotely identifying glaucoma via electronic transmission of high-resolution stereoscopic fundus photographs. Teleglaucoma is hypothesized as a more efficient way of managing glaucoma in rural areas, such as Alberta. Currently this technology is validated for use in diabetic retinopathy, but recent research has assessed its performance for glaucoma.[4] Teleglaucoma has the potential to reduce patient wait and travel times in rural areas as well as reduce the patient load in ophthalmic clinics. The first objective of this study is to synthesize the literature on teleglaucoma through a systematic review and conduct a meta-analysis to generate the diagnostic accuracy of teleglaucoma. The second objective is to assess the cost-effectiveness of teleglaucoma relative to in-person examination (standard of care).

1.1 Structure of thesis document

This thesis is presented in Integrated-article format in compliance with the standards outlined by Western University School of Graduate and Postdoctoral studies. Chapter 2 describes the background literature on glaucoma and teleglaucoma. The thesis consists

of two manuscripts. The first manuscript is “The effectiveness of teleglaucoma versus in-person examination (Systematic Review and Meta-Analysis)” and it comprises chapter 3. The second manuscript is “The cost-effectiveness of teleglaucoma versus in-person examination” and it comprises chapter 4. The first objective is addressed in chapter 3 and the second objective is addressed in chapter 4. Chapter 3 has recently been published in a peer-reviewed journal and publisher permissions have been granted to include the paper in this thesis (Appendix 1).[5] Portions of chapter 4 have been conditionally accepted for publication and is now under second review with PLoS ONE journal.[6] Chapter 5, the integrated discussion, summarizes the main results of the thesis and generates conclusions.

1.2 Literature Cited

1. Canadian National Institute for the Blind (CNIB) and the Canadian Ophthalmology Society (2009) Costs of vision loss in Canada. Access Economics Pty Limited Available: http://www.cnib.ca/eng/cnib%20document%20library/research/covl_full_report.pdf.

2. Rein DB, Zhang P, Wirth KE et al. (2006) The economic burden of major adult disorders in the United States. Arch Ophthalmol Dec; 124(12): 1754-60.

3. Hatt S, Wormald R, Burr J (2006) Screening for prevention of optic nerve damage due to chronic open angle glaucoma. Cochrane Database of Systematic Reviews Issue 4. Art. No.: CD006129. DOI:0.1002/14651858.CD006129.pub2.

4. American Academy of Ophthalmology. *Diabetic Retinopathy Preferred Practice Pattern Guidelines*. San Francisco, CA; 2008:39. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=d0c853d3-219f-487b-a524-326ab3cecd9a.

5. Thomas S-M, Jeyaraman MM, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

6. Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (*under second review 2015 June 7*).

Chapter 2 Literature Review, Thesis Rationale, and Thesis Objective

2.1 Literature review

2.1.1 Natural history of glaucoma

Glaucoma is an ophthalmic disease characterized by death of the optic nerve from excess fluid pressure in the eye. Increased pressure occurs when the trabecular meshwork can no longer drain excess fluid. Glaucoma is not a singular disease, but a collection of ophthalmic diseases with various clinical presentations that causes progressive optic neuropathy. They ultimately end in irreversible vision loss. Glaucoma is primarily categorized as either open or closed-angle glaucoma:

Open-angle glaucoma (OAG) is the most common type of glaucoma; 90% of glaucoma cases are open-angle.[1] It is caused when the drainage canals clog and intraocular pressure rises. The angle between the cornea and iris becomes wide and open. Open-angle glaucoma is also called primary or chronic glaucoma. It slowly develops and symptoms are not noticed until advanced stages. Glaucoma presents as mild, moderate, and severe stages. The outer nerves of the eye are damaged first and causes vision loss starting at the edges of the eye. As it progresses, vision is lost inward producing “tunnel vision”. Because of this, many glaucoma patients do not notice their vision loss until the advanced stages of glaucoma. It is estimated that 50% of those with glaucoma are unaware of their disease status.[2] The focus of this thesis is OAG.

Close-angle glaucoma is also caused by blocked drainage canals and results in increased intraocular pressure. The angle between the iris and cornea becomes narrow or closed. Unlike open-angle glaucoma, it develops quickly and vision

loss is very noticeable. Closed-angle glaucoma requires immediate medical attention.[1]

2.1.2 Risk Factors

Intraocular pressure

Intraocular pressure (IOP) is one of the main characteristics of glaucoma. Normal IOP are pressure levels that do not lead to optic nerve head damage and average between 12-22 mm Hg.[3] As it is measurable, it is a quantitative measure used to determine glaucoma, but it cannot solely be used for diagnosis. IOP is affected by several factors including genetics, environment, physiology, ethnicity, refractive error, and diurnal and postural variations.[1,4,] These factors on their own can be considered risk factors for glaucoma. Several genetic studies such as the Blue Mountains Eye study and Beaver Dam Eye Study have identified chromosomal locations responsible for fluctuations in IOP.[1,5,6] Links between myopia and closed-angle glaucoma in adults are not definite; some studies have reported either positive or no associations.[1] One of the main factors affecting IOP and contributing to glaucoma is systemic conditions such as diabetes mellitus, and hypertension. Smoking, drug use, and dietary exposures can affect IOP. Smoking can lead to vasoconstriction and increased episcleral venous pressure. Use of anesthesia drugs (eg. ketamine), illicit drugs (eg. LSD), and systemic medications (eg. corticosteroids, anticholinergic agents, sulfonamides) may elevate IOP.[1,4] Dietary exposures have not been studied thoroughly, but associations have been seen between caffeine consumption and increased IOP. Also, consumption of fruits, vegetables, and omega-3 fatty acids may reduce IOP.[1]

Age and Ethnicity

IOP tends to increase as people age naturally. Specifically adults older than 50 years are at higher risk of glaucoma.[4,7] The growth of crystalline lens increases as people age. This causes the anterior chamber to become crowded and closes the angle within the eye. The risk of glaucoma increases after the age of 40 years.[4] The Baltimore Eye Survey found those who are 70 to 79 of age have a 3.5 times higher prevalence than those in between 40 to 49 years of age.[4,8] Edgar et al reported in those aged 50-59 years, the prevalence of open-angle glaucoma in Black populations was 4.6%, in Asian populations was 1%, and in Caucasian populations was 0.8%.[9] There was an increased prevalence in all races with increased age: for ages 60-69 years, the prevalence was 7.2% in Black populations, 1.6% in Asians, and 1.6% in Caucasian populations, and for ages 70-79 years the prevalence was 16%, 3%, and 6%, respectively.[9] In older age groups, women tend to have greater IOP than men specifically after the onset of menopause.[9]

Ethnicity can affect IOP. Black populations have been found to have higher IOP and at greater risk for open-angle glaucoma.[1,2,9] The Baltimore Eye Survey found that black populations have three to four times greater prevalence than Caucasians.[8,9] Nonetheless, studies have found Asian populations have increased risk of closed-angle glaucoma.[9,10] Further trends based on ethnicity are detailed in the *Epidemiology* section.

2.1.3 Epidemiology

Glaucoma is the leading cause of permanent blindness in Canada affecting more than 400,000 Canadians and 67 million people worldwide.[2] Glaucoma is accountable for 14% of all blindness cases.[1]

Over the past decade there has been several population-based prevalence surveys of glaucoma globally.[1,5,6,8] Of individuals aged 30 years or more, the prevalence of open-angle glaucoma ranges from 0.03% in China to 8.76% in St. Lucia.[9] The prevalence of glaucoma is increases as people get older. Glaucoma is more prevalent in certain races. In Caucasian populations, the prevalence of open-angle glaucoma in those older than 40 years, is approximately 2%.[9] However, it has been reported that Caucasians of comparable age groups have the same prevalence.[9] In contrast, there was higher prevalence in similar age groups reported in Black populations in the Caribbean and North America.[9] In North America, the highest prevalence is seen in the African-American population, at 8%.[9] The age-adjusted rates were 4.3 times higher in African-Americans than Caucasians Americans.[9] In addition, the age of onset is earlier in African-Americans than in Caucasian Americans.[9] The prevalence of glaucoma is higher in Black Caribbeans than in African-Americans and black populations in Africa. Specifically, Caribbean countries such as St. Lucia and Barbados have reported the highest prevalence rates within the Caribbean.[9,11] Significant glaucoma studies were completed in these countries such as the Barbados Eye Study.[9,11]

In Asian populations, closed angle glaucoma are more common with a prevalence of 1%, while the prevalence of open-angle glaucoma is only 0.31%.[9]

However, variability has been reported. In Japan, the prevalence of open-angle glaucoma is greater than closed-angle glaucoma (2.53% versus 0.08% respectively).[9]

The prevalence differs also for open-angle and closed-angle glaucoma. Open-angle glaucoma is most common form of glaucoma in European, Africans, and North Americans.[9]

The incidence of glaucoma is 0.04% and 4 out of every 10,000 persons at any given time will develop glaucoma.[4] Studies have reported increased incidence with age: the five year incidence for those aged 55 years was 0.2% and it increased to 1% for those aged 75 years.[9,12,13] Another study reported the annual incidence in those aged 60-69 years was 12 per 10,000, in those aged 70-79 years incidence was 28 per 10,000, and for those aged 80 years and older incidence was 82 per 10,000.[4] Specifically for black populations, the 4-year incidence reported was 55 per 10,000.[4]

2.1.4 Clinical Assessment of Glaucoma

Glaucoma diagnosis requires several diagnostic tests and imaging based on the following key characteristics of glaucoma: visual field, intraocular pressure, and optic nerve head. Each of the key characteristics of glaucoma and the required diagnostic tests are described in details below.

Visual Field

Changes in visual field can be used to help detect glaucoma. Visual field loss in an eye that previously did not have visual field loss can indicate glaucoma. Also, progressive visual field loss in an eye with previous loss is an important factor. Visual field defects associated with OAG glaucoma are paracentral defects, arcuate defects, and nasal steps, as well as, depression in sensitivity, blind spot baring, and increased blind spot. The main detection technique used is visual inspection followed by comparison to normal visual field charts. Visual field loss is scored using the Glaucoma Hemifeld Test (GHT) or Humphrey Visual Field Analyzer (HFA).[4]

Intraocular Pressure (IOP)

IOP is measured using a tonometer. Applanation tonometry uses the Inbert-Fisck law which states IOP is equal to the weight applied to the cornea divided by the applanated area.[1] There are two main tonometers: indentation and applanation. Indentation tonometer has a truncated cone shape and it displaces larger intraocular volume. Empirical data is used to create a conversion table to measure the IOP. The second type, the applanation tonometers, has a flattened shape deformation and the relationship to the IOP can be used to measure the IOP. The applanation tonometer measures the force that is required to flatten the corneal surface area. This is called the Goldman applanation tonometer. The Goldman applanation tonometer is widely used for measuring IOP. It is attached to a slit lamp and it is used to display the circular area of the cornea into semicircles.[1]

Another classification of tonometers are contact and non-contact tonometers. The Goldman applanation tonometer is a contact tonometer. The probe of the tonometer comes into contact with the cornea and as a result a topical anesthetic is used. The anesthetic is applied as an eye drop to the surface of the eye. An example is proxymetacaine.[1]

Non-contact tonometers do not come into contact with the eye and instead uses a puff of air to deform the cornea. It determines the time and the force of the air-puff that is needed to flatten the cornea. It uses an electro-optical system to detect applanation. The force detected is used to estimate the IOP. Historically, the accuracy of non-contact tonometers have been incomparable to contact tonometers and thus, it was a convenient method for screening IOP. With advances in technology, however, current non-contact tonometers have correlated higher with the contact tonometers.[1]

Optic Nerve Head

The optic nerve is responsible for sending visual information from the eye to the brain and it is located at the back of the eye. The optic nerve head, also known as the optic disc, is the main pathological feature associated with glaucoma. It is the distal portion of the optic nerve, which extends from the retinal surface to the myelinated portion of the optic nerve.[1] Retinal nerve fibers converge upon the optic nerve head which continues to the brain. The optic nerve head is susceptible to elevation of IOP. Progressive atrophy of the optic nerve head and loss of optic nerve fibers characterize glaucoma. The optic nerve head is normally shaped with a vertical ovoid referred to as a cup. The relationship between the diameter of the cup and the diameter of the whole

optic nerve head is used to diagnose glaucoma. This relationship is called the cup-to-disc ratio (CDR).[4] Glaucoma increases the size of the cup in a vertical oval-type pattern thereby increasing the CDR. Defects of the optic nerve are called cupping or a cupped nerve. One issue with using the CDR is that even within healthy eyes the values may range. One source reported the CDR of a healthy eye as approximately one third.[16] Another reported the average horizontal and vertical CDR as 0.5 and 0.42 respectively.[4] There are specific variations within race where African-Americans have significantly larger CDR than Caucasians.[4]

Stereoscopic photos of the optic nerve are taken to evaluate for glaucoma. In addition to the CDR, the ophthalmologist uses the neuroretinal rim and the nerve fiber layer (NFL) of the optic nerve to determine optic nerve damage. Specifically, the thickness of neuroretinal rim and NFL should be greatest inferiorly and then the superior, nasal, and temporal rim; this is known as the ISNT rule.[4] Deviation from this rule is a sign of potential glaucoma. Notching of the neuroretinal rim and/or a thin or sloped temporal rim are also associated with glaucoma. Thinning of the NFL can be associated with hemorrhaging. Disc hemorrhaging is seen in 40% of all glaucoma patients.[4] This occurs usually before the neural rim notching or nerve fiber layer and visual field defects. The hemorrhaging is a result of the glaucomatous damage rather than a cause. Another sign of glaucomatous damage is the asymmetry of the optic nerve head between the eyes. Healthy eyes will have no more than a 0.2 difference between the CDR of the right and left eye.[4]

The traditional instrument for physically examining the optic nerve is the direct ophthalmoscope. However, it can only generate two-dimensional images, which are difficult to assess surface contours. Slit-lamp bio-microscope with handheld lens is the preferred instrument to physically examine the optic nerve.[1,4] Additionally, optic disc stereophotography is used to monitor changes of the optic nerve by comparing older to recent photographs. Optic nerve head hemorrhaging, notching, neuroretinal rim loss, and vessel barring can all be seen with optic disc stereophotography.

Optic nerve imaging uses technologies called GDx nerve fiber analyzer, Heidelberg Retinal Tomography (HRT), and Optical Coherence Tomography (OCT).

GDx nerve fiber analyzer is a scanning laser polarimetry and it measures the peripapillary retinal nerve fiber layer thickness. It sends laser beams to the posterior retina and it uses the changes in the retardation of the reflected beam for creation of a high-resolution image of the optic nerve and peripapillary retina. This techniques measures the retinal nerve fiber layer (RNFL) thickness. A graphical plot of the RNFL thickness around the optic nerve, called the double hump, is determined along a 3.2 mm diameter 8-pixel wide circle.[4,15,16] In healthy eyes, the superior and inferior poles have the largest RNFL thickness compared to the nasal and temporal poles.[4,15,16]

Heidelberg Retinal Tomography (HRT) uses scanning laser tomography to produce 3-dimensional high-resolution image of the optic nerve.[17] HRT provides precise measurements of optic nerve head parameters that can be used to identify nerve fiber damage and loss. It uses laser beams to shine light and scan different areas of the retina.[18] The computer develops a calculated image that is used to produce

measurements of morphometric parameters of the disc.[1] This information is used to classify the nerve as normal or glaucomatous and to measure the disease progression. A reference ring is placed on the image to define the retinal surface. The cup is the structure located below the reference plane and the rim is the structure above the reference plane or within the contour lines. To measure the RNFL thickness, HRT uses the distance between the reference plane and the retinal surface.[4,18] Moorfields regression analysis uses the ratio of the rim area to the disc area to determine the appearance of the optic nerve head as “normal,” “borderline,” and “outside normal limits.”[1,4]

Optical Coherence Tomography (OCT) is an imaging technique that applies the concepts of interferometry. It uses a low-coherence infrared diode light source that splits into two beams and travels perpendicular to each other. The light is then reflected with the eye and intersects with the reference beam. The point of intersection creates an interference signal, which is detected by the interferometer. These signals are then used to create a cross-sectional image of the retina. The RNFL thickness is measured by the difference in the delay of backscattered light from the RNFL inside the imaged tissue.[1] This test is non-invasive, involves no contact, and is trans-pupillary. With OCT, a linear scan of the retina is performed in 1 second while the pupils are dilated.[1] The images created give the average RNFL thickness in micrometres. Another image of the retinal displays a colour-coded map of the retinal fibre layers (Figure 1).[19] Unlike the healthy retinal fibre layers shown in Figure 1, a glaucomatous OCT will display a cupping form within the layers. The OCT can provide measurements of the cup area, disc area, and cup-to-disc ratio. Comparative images of the left and right eye are

created to compare the RNFL of both eyes and to analyse the symmetry between eyes. Asymmetry between the eye can be a sign of glaucomatous loss.[20]

2.1.5 Glaucoma Screening

Screening and diagnostic tools are significant to prevent glaucoma from progressing to advanced stages and maintaining healthy vision.[21] In addition, glaucoma prevention will minimize future healthcare costs. The total cost of glaucoma treatment is estimated to be $1480 for mild, $3682 for moderate, and $4975 for severe forms of glaucoma.[22] Screening can improve the efficiency of the health care system by increasing the number of patients accessing ophthalmic services and reducing the number of false-positive referrals to ophthalmologists.[23]

The standard of care for glaucoma screening consist of routine optometrist visits every 2-3 years and any glaucoma suspect patient will be referred to an ophthalmologist for additional diagnostic testing.[24] Those of older ages are at a greater risk of glaucoma and thus ophthalmologists recommend routine optometrist visits every 2 to 4 years for adults between 40 to 64 years and every 1 to 2 years when aged 65 and older.[21] Patients regularly seen by an ophthalmologist for other ocular conditions may also be referred for glaucoma diagnostic testing if symptoms appear. In-patient examination will be referred to as “in-person” examination. In-person examination for glaucoma (passive “in-person screening”) is performed at specialized clinics and includes detailed history, slit lamp examination, visual field testing, and fundus photography performed by the optical technician followed by consultation with the ophthalmologist.[25,26] This is considered no-screening or the “do-nothing” approach where glaucoma suspects go to

in-person care when symptomatic. The “do-nothing” refers to that fact that the healthcare providers are not actively searching for potential candidates to screen. Patients go to visit the optometrist or ophthalmologist when they feel necessary. In contrast, “active screening” refers to teleglaucoma screening where healthcare providers actively seek people at-risk of glaucoma within the general population and these people are encouraged to be screened.

2.1.6 Teleglaucoma Screening

Teleglaucoma is a relatively new screening and diagnostic tool for targeting remote or under-serviced communities. It uses stereoscopic digital imaging to take ocular images, which are transmitted electronically to an ocular specialist. The ocular specialist will then assess the images, identify risk factors, and diagnose for glaucoma. If necessary, the ocular specialist will refer identified glaucoma cases for medical consultations or to ophthalmologists for follow-up treatment. Unlike other teleophthalmology tools, teleglaucoma requires more sophisticated diagnostic tests. The main tests are optic nerve photographs, Optical Coherence Tomography (OCT), Intraocular Pressure (IOP) measurements, central corneal thickness (CCT) measurements, and visual field tests.[27-29] The combination of examinations and equipment required can vary based on organizational resources, target goals, and populations. However, the more diagnostic tools used during screening for glaucoma the greater the accuracy and effectiveness of the screening process. The equipment required for teleglaucoma are the ophthalmic examination equipment, cameras, and

computer imaging software. The full list of the standard equipment and components of teleglaucoma can be found in Table 1.[27-29]

Several studies have reported on the effectiveness of teleglaucoma. Teleglaucoma technology demonstrated moderate agreement in its ability to diagnose glaucoma (Kappa statistic 0.55% [0.48, 0.62]).[30] When disc damage had Vertical Cup to Disc Ratio (VCDR) greater than 0.7 the Frequency Doubling Technology (FDT) had a substantial agreement with the ability to diagnose glaucoma (kappa statistic 0.84).[30] In addition, a study conducted in rural India compared the ability of teleglaucoma to detect glaucoma compared to standard in-clinic examination and found that there was a good agreement in detecting glaucoma. For glaucoma the kappa scores were 0.61 with standard screening versus 0.59 for teleglaucoma.[31] In comparison to the in-person slit lamp examination, the positive predictive value was 77.5% for positive teleglaucoma diagnosis and it had a negative predictive value of 82.2% for negative teleglaucoma diagnosis.[30] This suggests that the probability of a positive test in a glaucoma positive case is 77.5%. Also, the probability of a negative test in a glaucoma negative case is 82.2%. However, a cohort study conducted by the University of Alberta found 24% of teleglaucoma photographs were deemed unreadable from media opacities, patient cooperation, and unsatisfactory photographic techniques.[30]

The advantages of teleglaucoma include convenience, decreased travel time to medical clinics, increased access to specialized care for glaucoma, and decreased patient costs. The benefits are mainly seen in remote or under-serviced communities such as Aboriginal communities, rural Manitoba, as well as Alberta where there is

limited ocular specialists. Teleglaucoma wait time reduction was 41% versus 19% with in-person examinations.[32] Arora et al. reported improved access time (time from patient being referred to the date visit is booked) of 45 days with teleglaucoma versus 88 days for standard in-person examinations.[38] Teleglaucoma had reduced cycle time (time from registration until patient leaves clinic) of 78 minutes versus in-person exam of 115 minutes.[32] The pioneer teleglaucoma study conducted in Finland reported reduced absence from work by 50% with teleglaucoma versus in-person examination, and in addition reduced traveling (97%), costs (92%), and time (92%).[33]

2.1.7 Systematic Review

The purpose of systematic reviews (SR) is to synthesize research literature from published and unpublished sources about a research topic.[34] There are several steps in the process of conducting a systematic review.[34,35] First is to define the question. It is important to specify the inclusion and exclusion criteria, the population, the intervention, the outcome, and methodology. The second step is to conduct the literature search. This involves choosing information sources both published and unpublished sources and identifying titles and abstracts. Once the articles are generated and organized into the database the articles are then screened using the inclusion and exclusion criteria. Level 1 screening is applied to titles and abstracts. Level 2 screening involves obtaining full text articles for eligible studies and applying the inclusion and exclusion criteria. Two reviewers conduct the screening. At each stage, the reviewers compare agreements and disagreements to ensure article eligibility. If disagreements occur, then a third reviewer intervenes and makes the decision. The fourth step is to create a database

with important study variables. The data extraction is then conducted and information is collected on each study's population, interventions, comparison, and study design. In addition, other study variables include the results, methodologic quality, and validity agreement. The last step is to conduct the analysis and generate pooled estimates. It is important to assess variability amongst studies, which is the level of heterogeneity. Publication bias, a common bias affecting systematic reviews, is the selective publication of studies. Publication bias is tested using funnel plots.

Systematic reviews are useful for determining if study results are valid. It analyzes the methodologic quality of studies and it examines the reproducibility of studies. It summarizes the results and determines if there is variability in study results. It also gives the precision of results.[35] The significance of systematic reviews is that it gives the summary of all research literature in one document. This makes it easy for clinicians, policy makers, and healthcare care administrators to be informed of the evidence. It provides pooled estimates necessary for decision makers to make evidence-based decisions. Systematic reviews are useful for determining important patient outcomes and furthermore, how to apply the results to patient care.

2.1.8 Meta-analysis

Meta-analysis are a continuation of systematic reviews that add precision to the synthesized results. They are a formal, quantitative study to assess the strength of existing evidence on the specific research question. The meta-analysis is beneficial to determine if a treatment effect exists, if the effect size is positive or negative, and the relative treatment effect in comparison to the comparator.[36]

The statistical analysis involves the calculations of effects sizes in forms of risk ratios, odds ratios, and standardized mean differences depending on the exact study purpose. Studies are weighted for analysis based on the value of the evidence in each study and its sample size. More specifically studies are weighted according to the inverse of their variance.[36] Thus, studies with smaller sample sizes will contribute less to the pooled estimate of effect size. There are two main models used in meta-analysis when generating the effect sizes: fixed effects and random-effects models.[36] In the fixed-effects model, the source of variation in study results occurs from within each study. This model is homogenous, which means that the study treatments, populations, and other study variables are the same amongst studies. In contrast, the random-effects model assumes there is heterogeneity among study results. Studies are weighted by the inverse of their variance and the heterogeneity parameter.

Hierarchical logistic regression model is another model that incorporates aspects of both fixed-effect and random-effect models.[37] It is used for mixed models that have a group structure.[38] The theory of hierarchical modelling is that at the micro level the normal logistic regression is used, but the coefficients may vary for each macro level observation. At the macro level, the micro level coefficients are functions of the macro level regression.[39] Hierarchical models are useful for multilevel analysis where there is within study variance, as well as, between study variance.[39] This is because hierarchical models are good for modelling specificity and sensitivity. This model is also useful for measures with binary responses. In addition, it is useful for meta-analyses as it takes into consideration the effects of study-specific covariates.

From the hierarchical regression modeling a Hierarchical Summary Receiver Operating Curve (HSROC) is generated, which provides the accuracy of the screening tool. It graphs both sensitivity and specificity to give a pooled estimate from all of the reported study estimates. The pooled estimate lies within a line or curve called the "summary line".[40] Summary lineis used when there are no covariates and is calculated using parameters from the bivariate model. The summary line shows the range of the pooled estimates of sensitivity and specificity separately, and it represents the relationship between specificity and sensitivity.[40] Therefore, it demonstrates how changing the summary specificity affects the summary sensitivity.

Both the summary estimate and the summary line are interpreted against the clinical threshold to determine if the screening tool is accurate or not. Firstly, the curvature of the line is important; if there is a positive upward slope, this shows there is a positive relationship between specificity and sensitivity.[40] Secondly, the area under the curve represents the accuracy. The greater the area under the curve the higher the accuracy. Generally, if the HSROC lies above the threshold line, which lies at a 45 degree angle, then the accuracy is better than random chance.[40] Also, if the HSROC lies above the clinical threshold stipulated by physicians or health experts then that screening tool is deemed clinically acceptable.[40]

The HSROC curve also provides the 95% confidence region which is the confidence interval of the summary estimate. The confidence region is the range of estimates that are likely to include the true estimate with 95% probability.[41] HSROC also gives the 95% prediction region, which is the region that the future observation will fall

given the existing data with 95% probability.[41] Both measures are useful for researchers and clinicians to understand the distribution of the data, and the predicted data. It also gives the statistical significance of the summary estimate. The wider the confidence or prediction regions, the less statistically significant the summary estimates.

One of the benefits of meta-analysis is it assesses the sources of heterogeneity among studies.[35] Note, one of the purposes of meta-analyses is to determine which treatment/intervention is more effective. Thus, identifying the sources of heterogeneity can assist in interpreting the results and generating the conclusions of the meta-analysis. Study results should be interpreted with caution when heterogeneity, the variation among studies, exists.[36] This may call for subgroup analysis to determine the factors or covariates affecting the study results.

There are two kinds of variability in studies: clinical diversity and methodological diversity.[36] Clinical diversity is the variability in the study's population, intervention, and/or measures. Whereas, methodological diversity is the variability in the study design and its related risks of bias.

Heterogeneity is quantified using the inconsistency index I^2. The I^2 is given by a percentage of total variation across studies and ranges from 0 to 100%.[35,36] If I^2 is greater than 75% then there is substantial heterogeneity amongst studies.[35,36]

Both systematic reviews and meta-analysis have been used extensively in ophthalmology to synthesize ophthalmic literature on glaucoma, diabetic retinopathy, cataracts, and all other eye diseases. They have been applied to determine the

effectiveness of many interventions including the effectiveness of screening strategies. The Cochrane Review has published a systematic review on the effectiveness of screening for glaucoma and found that screening is effective in glaucoma populations specifically when targeting at-risk population.[21]

Several systematic reviews and meta-analysis have been conducted on teleophthalmology use for diabetic retinopathy, however, no studies have looked at the literature on teleglaucoma as discussed earlier.

2.1.9 Specificity and Sensitivity

The two main measures of screening effectiveness are specificity and sensitivity. Both are independent of the population or prevalence. Specificity is the ability of the test to correctly detect the people who do not have the disease.[40] Statistically it is calculated by the number of negative tests divided by those without the disease.[42] The denominator are those without the disease which include both the true negatives cases who test negative (true negatives) and the negative cases who test positive (false positives).

Sensitivity is the ability of the test to correctly detect positive cases in those with the disease.[40] The higher the sensitivity the more effective the test is at detecting positive cases. Statistically, it is calculated by the number of true positives tests divided by the number of people with the disease.[42] Likewise, the denominator are those with the disease which include both the true positive cases who test positive (true positive) and the true positive cases who test negative (false negatives).

For teleglaucoma, both the sensitivity and specificity are important; it is good practice to detect both the negative and positive cases correctly for efficient patient care and patient health outcomes. However, the sensitivity of teleglaucoma is particularly important because it incorporates the false negatives.[42] The false negatives are the patients who have the disease and are incorrectly detected as a negative test. This patient group will be told they do not have the disease and continue living as normal. However, with glaucoma, this is particularly crucial to avoid. Glaucoma is a silent thief of vision and if left untreated patient can lose substantial visual acuity as well as suffer from visual defects. Thus, the sensitivity of teleglaucoma is important to prevent glaucoma cases from leaving the clinic without appropriate medical care.

2.1.0 Cost-Effectiveness Analysis

Economic evaluations are an essential part of healthcare. Specifically, cost-effectiveness analysis (CEA) is an economic evaluation used by policy makers and healthcare administers to make decisions in healthcare.[43] Directions in health care, as well as other areas of the public sectors, are based primarily on funding and the expected benefits.[43,44] Hence, CEA describes the relationship between the costs and the effects (expected benefits) of interventions. CEA provides the evidence of where healthcare funds should be applied. Thus, the significance of CEA is that, it determines resource allocation and which health programs/interventions are funded.

In terms of ophthalmology, CEA is useful for comparing the costs and effects of different treatments for glaucoma, diabetic retinopathy, cataracts, etc. This economic evaluation can help determine which intervention is cost-effective and should be implemented. In addition, the beauty of CEA is that it can use quality of life measures as the effect data, such as quality-adjusted life years (QALY) or utility values.[43] Thus, an intervention in glaucoma that increases the visual field by 15% which is equivalent to improvement of 0.12 QALYs, is equivalent to a cardiac intervention that reduces blood flow by 0.02%, which is also equivalent to a 0.12 QALY improvement. This allows comparison of ophthalmic interventions to non-ophthalmic interventions. Thus, CEA provides healthcare administrators and policy makers' essential tools to allocate resources among different health care areas.[43] CEAs can generate conclusions on the benefits to the health care system and improvements in health service quality. More specifically, glaucoma is a chronic and progressive disease. As discussed earlier, there is no cure for glaucoma, hence the cumulative cost of living with the disease increases as patients live longer with the disease and increase substantially as the patients progress to advanced stages. CEA can be beneficial at assessing the long term costs and benefits associated with glaucoma.[44] It is important to know the long term benefits after interventions for glaucoma are implemented. Also, CEAs can provide the long term patient health outcomes and its associated costs, which is essential to health care planning.

2.1.11 Conclusion

Overall, teleglaucoma has potential to increase the access to ophthalmic care in rural and under-serviced areas where there is either limited ophthalmologists or requirement of a long travel. It is predicted that with teleglaucoma, there will be increased quality of life in patients with glaucoma. With progressive permanent vision loss as the main factor affecting a patient's quality of life, detecting glaucoma patients through screening can assist to prevent vision impairment.

2.2 Thesis Rationale

Current health reforms are shifting towards "e-health;" the incorporation of technology within healthcare to bring together distant communities and to improve access to expert medical advice and diagnosis.[45,46] Telemedicine facilitates communications across geographic borders and across interdisciplinary networks. In many areas of health care, telemedicine has allowed more informed decision making and improved quality of care.[45-48] It is efficient and convenient and it has benefits to improving the efficiency of administration.[47,48] Telemedicine has demonstrated cost-effectiveness in delivery of care for other health diseases.[45,46] Specifically, rural and elderly populations both benefit from remote in-home consultation.[47,48]

The use of telemedicine in ophthalmology (tele-ophthalmology) is not a new concept. Several studies have examined the use of tele-ophthalmology for screening of

diabetic retinopathy and found tele-ophthalmology played an effective role in screening diabetic retinopathy.[49-542-57] However, few studies have examined the use of tele-ophthalmology for glaucoma screening, in terms of its sensitivity, specificity, and time-savings.

Tele-ophthalmology is an emerging screening technique that can be effective for glaucoma detection for several reasons. Firstly, glaucoma is an age-related disease affecting the elderly populations. Teleglaucoma allows remote consultations which reduces travel time, and thus, the elderly population may benefit from the convenience of teleglaucoma.[45,48,49] It promotes senior wellness and improved quality of life for the elderly. Secondly, glaucoma causes peripheral vision loss initially as opposed to diminishing visual acuity. As a result, patients may not notice visual field defects initially. It has been reported that 50% of cases are not detected until the advanced stages of the disease.[2] Introduction of teleglaucoma can detect cases that may not have been detected otherwise.[28] It is hypothesized that screening of elderly populations and populations at-risk will detect potential cases and cases at earlier stages of the disease. In addition, vision loss and visual defects due to glaucoma are permanent. Teleophthalmology would be beneficial to glaucoma patients as it can capture cases earlier thereby avoiding vision loss and permanent blindness. In return, preserving vision through teleglaucoma will improve the quality of life of patients. Therefore, the thesis rationale is that tele-ophthalmology may have a significant contribution for glaucoma management and have a significant impact on glaucoma patients.

Research has been conducted on the effectiveness of teleglaucoma and the direct benefits to patients and the healthcare system. However, to date, there is no synthesis of the research data. Synthesized effectiveness data is required to make informed decisions and to implement this technology for glaucoma screening. Healthcare decisions are based on research evidence. In addition, there are cost implications for implementing teleglaucoma. Research on the cost-effectiveness of teleglaucoma has not been published in research literature. This thesis will contribute to research literature by synthesizing the data on the effectiveness of teleglaucoma and analyzing the cost-effectiveness of teleglaucoma.

2.3 Thesis Objectives

There are two objectives of this thesis. The first objective is to determine the effectiveness of teleglaucoma in-comparison to standard in-person examination for glaucoma screening. This thesis will synthesize information on diagnostic accuracy, benefits to health care service quality, and improvements to patient quality of life. The second objective is to determine the cost-effectiveness of teleglaucoma in rural areas for at-risk populations.

2.4 Literature Cited

1. Allingham, R. R., Damji K, Shields, M. B. et al. (2011). *Shields' textbook of glaucoma*. 6th ed. Philadelphia: Lippincott Williams & Wilkins.

2. Varma R, Lee P, Goldberg I, et al. (2011) An Assessment of the Health and Economic Burdens of Glaucoma. Am J of Ophthalmol 152(4):515–522. doi: 10.1016/j.ajo.2011.06.004

3. Glaucoma Research Foundation (2008). High Eye Pressure and Glaucoma. Available: http://www.glaucoma.org/gleams/high-eye-pressure-and-glaucoma.php. Accessed 2014 June 23.

4. Gupta, D. (2005). Glaucoma diagnosis and management. Philadelphia: Lippincott Williams & Wilkins

5. Mitchell P1, Smith W, Attebo K, et al. (1996) Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology. 1996 Oct;103(10):1661-9.

6. Klein BE1, Klein R, Sponsel WE, et al. (1992) Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology. 1992 Oct;99(10):1499-504.

7. Tombran-Tink J, Barnstable C, Shields M, et al. (2008). Mechanisms of the Glaucoma: Disease Processes and Therapeutic Modalities. New Jersey: Humana Press, Springer Science & Business Media.

8. Sommer A. (1996). Glaucoma risk factors observed in the Baltimore Eye Survey. Curr Opin Ophthalmol. 1996 Apr;7(2):93-8.

9. Edgar, D. F., & Rudnicka, A. R. (2007). Glaucoma identification and co-management. New York; Edinburgh: Butterworth-Heinemann/Elsevier.

10. Cheng JW, Zong Y, Zeng YY, et al. (2014) The prevalence of primary angle closure glaucoma in adult Asians: a systematic review and meta-analysis.

11. Leske MC, Connell AM, Schachat AP, et al. (1994) The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol. 1994 Jun;112(6):821-9.

12. Hiller R, Podgor MJ, Sperduto RD, et al. (1999) High intraocular pressure and survival: the Framingham Studies. Am J Ophthalmol. 1999 Oct;128(4):440-5.

13. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol. 1966 Oct;50(10):570–586.

14. Glaucoma Research Foundation (2005) How glaucoma affects the optic nerve. Available: http://www.glaucoma.org/glaucoma/the-optic-nerve-questions-and-answers-from-dr-bradley-schuster.php Accessed 2014 July 29.

15. Solish S, Miller A, Aref A et al. (2010) Optic Nerve and Retinal Nerve Fiber Imaging. EyeWiki. Available: http://eyewiki.aao.org/Optic_Nerve_and_Retinal_Nerve_Fiber_Imaging#Optic_Nerve_Imaging_Technologies Accessed 2015 Jan 10.

16. Salmon J (2003) Glaucoma: a colour manual of diagnosis and treatment. 3rd ed. Oxford: Butterworth-Heinemann.

17. Morrison, J. C., & Pollack, I. P. (2003). Glaucoma: Science and practice. New York: Thieme Medical Publishers.

18. Edward, D. P., & Vajaranant, T. S. (2013). Glaucoma. Oxford: Oxford University Press.

19. Klevering J (2011). Interpretation of the OCT Image. University Medical Centre Nijmegen. Available: http://www.slideshare.net/drscaliskan/nterpretation-of-optic-coherence-tomography-images Accessed 2014 Aug 3.

20. Grehn, F., Stamper, R. Springerlink (2006). Glaucoma. Berlin, Heidelberg: Springer-Verlag Berlin Heidelberg. doi:10.1007/3-540-34773-9

21. Hatt S, Wormald R, Burr J (2006) Screening for prevention of optic nerve damage due to chronic open angle glaucoma. Cochrane Database of Systematic Reviews Issue 4. Art. No.: CD006129. DOI: 0.1002/14651858.CD006129.pub2.

22. Lee PP, Walt JG, Doyle JJ, et al. A Multicenter, Retrospective Pilot Study of Resource Use and Costs Associated With Severity of Disease in Glaucoma. Arch Ophthalmol. 2006;124(1):12-19. doi:10.1001/archopht.124.1.12.

23. Shahid K, Kolomeyer A, Nayak N, Salameh N, Pelaez G, et al. (2012) Ocular telehealth screenings in an urban community. American Telemedicine Association. Telemed J E-Health 18(2): 95–100.

24. Canadian National Institute for the Blind (CNIB) and the Canadian Ophthalmology Society (2009) Costs of vision loss in Canada. Access Economics Pty Limited Available: http://www.cnib.ca/eng/cnib%20document%20library/research/covl_full_report.pdf

25. Glaucoma Research Society (GRS) of Canada (2014) Glaucoma. Available: http://www.glaucomaresearch.ca/. Accessed 2014 June 20.

26. Samples, J. R., & Schacknow, P. N. (2014). Clinical glaucoma care: The essentials. New York: Springer. doi:10.1007/978-1-4614-4172-4

27. Kassam F, Amin S, Sogbesan E, et al. (2012) The use of teleglaucoma at the University of Alberta. J Telemed Telecare 8: 367.

28. Amin S, Damji K, Kassam F, et al. (2012) In-house patient-centered teleglaucoma improves access and efficiency for glaucoma suspects and those with early stages of open-angle glaucoma (OAG). Canadian Ophthalmology Society Annual Meeting.

29. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

30. Kiage D, Kherani I, Gichuhi S, et al. (2013) The Muranga Teleophthalmology Study: Comparison of Virtual (Teleglaucoma) with in-person clinical assessment to diagnose glaucoma. Middle East Afr J Ophthalmol 20(2): 150–157.

31. Gupta S, Sinha SK, Dagar AB (2013) Evaluation of the effectiveness of diagnostic & management decision by teleophthalmology using indigenous equipment in comparison with in-clinic assessment of patients. Indian J Med Res 138: 531–5.

32. Arora, Rudnisky, Damji. Improved Access and Cycle Time with an “In-house” patient-centered teleglaucoma program versus traditional in-person assessment. Telemed J E Health 2014 [ePub ahead of print].

33. Tuulonen A, Ohinmaa A, Alanko H, et al. (1999) The application of teleophthalmology in examining patients with glaucoma: a pilot study. J Glaucoma 8: 367–73.

34. Gough D, Oliver S, Thomas J (2012) An Introduction to Systematic Reviews. London: Sage Publications Ltd, 304 pages. ISBN: 9781849201810

35. Guyatt G, Rennie D, Meade M, et al. (2008) Users' Guides to the Medical Literature: essentials of Evidence-Based Clinical Practice. 2nd edition (Jama & Archives Journals). McGraw-Hill. Professional.

36. Borenstein M, Hedges L, Higgins J, et al. (2009). Introduction to meta-analysis. Chichester, U.K: John Wiley & Sons.

37. Rutter CM, Gatsonis CA. (2001) A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001 Oct 15;20(19):2865-84. Available: http://www.ncbi.nlm.nih.gov/pubmed/11568945

38. Blei D. (2011) Hierarchical Models. Princeton University Oct 17, 2011 Course. Available: https://www.cs.princeton.edu/courses/archive/fall11/cos597C/lectures/hierarchical-models.pdf

39. Wong G, Mason W. (1985) The Hierarchical Logistic Regression Model for Multilevel Analysis. J Amer Stat Assoc. Vol. 80, No. 391 (Sep., 1985), pp. 513-524. Published by: Taylor & Francis, Ltd. on behalf of the American Statistical Association. Available: http://www.jstor.org/stable/2288464

40. Trikalinos TA, Balion CM, Coleman CI, et al. Meta-analysis of test performance when there is a "gold standard." AHRQ Publication No. 12-EHC080-EF. Chapter 8 of Methods Guide for Medical Test Reviews (AHRQ Publication No. 12-EHC017). Rockville, MD: Agency for Healthcare Research and Quality; June 2012. Available: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1101&pageaction=displayproduct.

41. Agostino R, Sulllivan L, Beiser A. (2006) Introductory Applied Statistics. Brooks/Cole Cengage.

42. Lalkhen AG, McCluskey A. (2008) Clinical tests: sensitivity and specificity. Cont Educ Anaesth Crit Care Pain. 8:221-223.

43. Drummond MF, Sculpher MJ, Torrance GW, et al. (2005) Methods for the Evaluation of Health Care Programmes, 3rd edition. Oxford University Press.

44. Gray AM, Clarke PM, Wolstenholme J, et al. (2010) Applied Methods of Cost-effectiveness Analysis in Health Care. Oxford University Press.

45. Ministry of Health Services and the Inter Tribal Health Authority (ITHA). (2011) Evaluation the Benefits. Telehealth – TeleOphthalmology. Available: https://www.infoway-inforoute.ca/en/component/edocman/1742-evaluating-the-benefits-telehealth-teleophthalmology-inter-tribal-health-authority-and-the-ministry-of-health-services/view-document Accessed 2014 Sept 24.

46. Ray KN, Demirci JR, Bogen DL, et al. (2015). Optimizing Telehealth Strategies for Subspecialty Care: Recommendations from Rural Pediatricians. Telemed J E Health. [Epub ahead of print]

47. Moffat JJ, Eley DS. (2010) The reported benefits of telehealth for rural Australians**.** Aust Health Rev**.** 34(3)**:**276-81.

48. Hailey D, Roine R, Ohinmaa A. (2002) Systematic review of evidence for the benefits of telemedicine. J Telemed Telecare. 8(suppl 1):S1.

49. Sanchez CR, Silva PS, Cavallerano JD, et al. (2010) Ocular telemedicine for diabetic retinopathy and the Joslin Vision nNtwork. Semin. Ophthalmol. 25 (5-6):218–224.

50. Aoki N, Dunn K, Fukui T, et al. (2004). Cost-effectiveness analysis of telemedicine to evaluate diabetic retinopathy in a prison population. Diabetes Care. 27(5):1095–101. Available at: http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22004000677/frame.html. Accessed 2014 July 23.

51. Wilson C, Horton M, Cavallerano J, et al. (2005) Addition of Primary Care-Based Retinal Imaging Technology to an Existing Eye Care Professional Referral Program Increased the Rate of Surveillance and Treatment of Diabetic Retinopathy. Diabetes Care. 28(2):318–322. Available at: http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.28.2.318. Accessed 2014 July 23.

52. Boucher MC, Desroches G, Garcia-Salinas R, et al. (2008) Teleophthalmology screening for diabetic retinopathy through mobile imaging units within Canada. Can. J. Ophthalmol. 43(6):658–68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19020631. Accessed 2014 July 22.

53. Zimmer-Galler IE, Horton M. (2013) Telehealth methods for diabetic retinopathy and glaucoma: Clinical, Technical and business insights and strategies for successful tele-ophthalmology programs. Association for Research in Vision and Ophthalmology (ARVO) Education Course. Association for Research in Vision and Ophthalmology Inc.1–117.

54. Bachmann M, Nelson S. (1996) Screening for diabetic retinopathy. A quantitative overview of the evidence, applied to the populations of health authorities and boards. Bristol Univ. Healthc. Eval. unit.1–57.

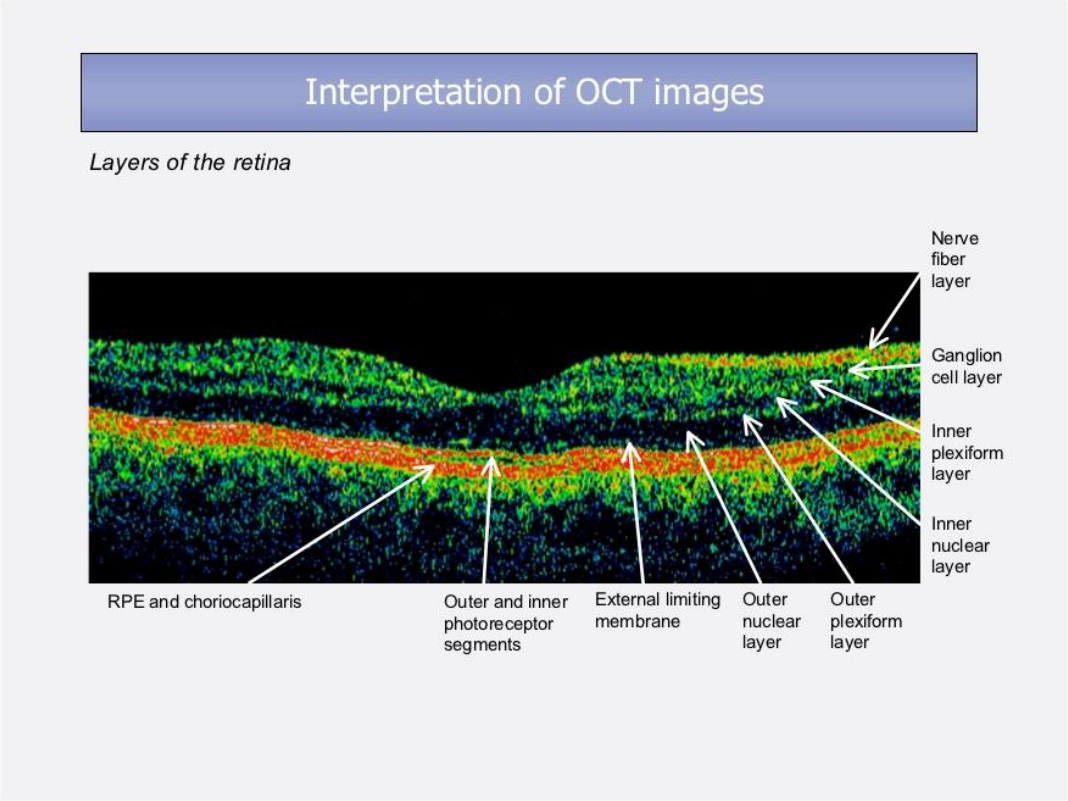
2.5 Tables

Table 2.1 Standard teleglaucoma equipment

Components	**Requirements**
Human Resources	Staff: graders, Ophthalmic technicians, nurses, optometrist, physicians, glaucoma specialists/ophthalmologists
Information Technology	Secure Diagnostic Imaging (SDI) system Videoconferencing equipment Computer systems and software ISDN installation
Screening Equipment	Retinal camera Tonometer Devices to measure central corneal thickness Frequency Doubling Technology (FDT) or Humphrey Visual Field test Optical Coherence Tomography Slit lamp Gonioscope
Examinations	Medical & family history Visual acuity IOP CCT Pupil equal and reactive to light (PERL) or relative afferent pupillary defect (RAPD) Slit lamp Gonioscopy Visual field Fundus photographs OCT Ancillary tests

2.6 Figures

Figure 2.1: OCT Image of a healthy retina[19]



Footnote: Morrison, J. C., & Pollack, I. P. (2003). Glaucoma: Science and practice. New York: Thieme Medical Publishers.

CHAPTER 3 The effectiveness of teleglaucoma versus in-person examination (Systematic Review and Meta-Analysis)

3.1 Introduction

Glaucoma is the leading cause of irreversible visual impairment in the world affecting 60.5 million people worldwide in 2010, which is expected to increase to approximately 79.6 million by 2020.[1] Therefore, glaucoma screening is important to detect, diagnose, and treat patients at the earlier stages to prevent disease progression and vision loss. Teleglaucoma uses stereoscopic digital imaging to take ocular images, which are transmitted electronically to an ocular specialist. Teleglaucoma involves standardized equipment (Table 1). The purpose is to synthesize literature to evaluate teleglaucoma, its diagnostic accuracy, healthcare system benefits, and cost-effectiveness. This chapter has been recently published.[2]

3.2 Methods

3.2.1 Search Strategy

A search methodology was used to assist in locating both published and unpublished studies. Research databases and conference meeting abstracts were searched for articles published from 1999 to current, and included MEDLINE (OVID and PubMed), Cochrane Library (Wiley), BIOSIS (Thomson-Reuters), CINAHL (EBSCO), Web of Science (Thomson-Reuters), and EMBASE (OVID). The grey literature was explored by searching Dissertations and Theses (ProQuest), the Canadian Health Research Collection (Ebrary), as well as the annual meeting abstracts of the European Society of Ophthalmology, Canadian Ophthalmology Society (COS), Association for Research in Vision and Ophthalmology (ARVO), and American Academy of

Ophthalmology (AAO). The Conference Proceedings Citation Index was also included as part of the Web of Science search. Hand searches of ARVO's *Investigative Ophthalmology & Visual Science* journal and *Canadian Journal of Ophthalmology* associated with COS were performed. The search strategies employed database specific subject headings and keywords for glaucoma, tele-screening, detection, and their synonyms. Each strategy was structured to accommodate for database and platform specific terminology, and syntax. The appendix contains the complete search strategies used for the various databases (Appendix 2). Alerts were set up for each database to receive publication notifications for new related articles.

3.2.2 Inclusion and exclusion criteria

Articles included were from any country, all in English, published from 1999 to current, and were research articles. The articles included a study population that consisted of adults in the general population or populations at risk of glaucoma. The study population included those with or without glaucoma. Articles on teleglaucoma intervention for glaucoma screening were included, both in-comparison to in-person screening and analyzing teleglaucoma on its own. Outcome measures of teleglaucoma articles selected contained efficiency measures, specificity, sensitivity, and its ability to detect glaucoma, as well as patient benefits and cost data. Economic evaluations such as cost-effectiveness analysis and studies with costing data were also included.

Specificity of teleglaucoma for this study was defined as the proportion of non-glaucoma cases who were correctly detected by teleglaucoma as a negative screen

test.[3] Whereas, sensitivity of teleglaucoma was defined as the proportion of glaucoma cases who were correctly detected by teleglaucoma as a positive screen test.[3] The proportion of true positive and negative cases are given through the diagnostic tests conducted by the ophthalmologist. Patients who were diagnosed by the ophthalmologists as glaucoma-positive were considered “true positives” and the patients who were diagnosed by the ophthalmologist as non-glaucoma cases were considered “true-negatives”.

The exclusion criteria consisted of articles published prior to 1999 since teleglaucoma is fairly new and to be consistent with the teleglaucoma screening procedure, year 1999 was selected as a cut-off year. Additionally, non-research articles such as methodology papers, editorials, review articles, commentaries, and letters were excluded. Articles on diagnosis or prognosis, genetic screening, and teleophthalmology for ocular conditions other than glaucoma were eliminated.

A total of 11,237 articles were retrieved by searching various databases and an additional 526 were retrieved from hand searching and grey literature search, which were then imported into EPPI 4.0 reference manager. Based on the inclusion and exclusion criteria, two reviewers independently reviewed all articles. After removing duplicate articles, 8157 articles were included for screening. Articles were screened by title, abstract, and full text in level 1, 2, and 3 screening, respectively. After each level of screening, kappa statistics was calculated to measure reviewer’s agreement. Additionally, if consensus was not reached by the two reviewers;’ then a third reviewer intervened to solve disagreements on article eligibility. The agreement between the two

reviewers was excellent (kappa = 0.86). The PRISMA diagram demonstrating the selection process is displayed in Figure 1.

3.2.3 Quality Assessment Strategy

Articles were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines for publication bias, risk of bias, imprecision, inconsistency, and indirectness.[4-9] Articles were graded as either low, moderate, or high quality of evidence. The results indicated that 17 articles were high quality, 13 were moderate quality, and 15 articles were graded as low quality of evidence. Despite the quality of evidence, all articles were included in the analysis.

3.2.4 Data Extraction Strategy

Qualitative and quantitative data necessary for the analysis was obtained from each article. Information on study location, design, effect measures (sensitivity and specificity), percentage of glaucoma diagnosed, service times, image quality, visual acuities, ophthalmic characteristics, and costs were collected. One reviewer extracted data using an excel template. Authors were emailed to obtain missing relevant information. All databases were updated with new information from respective authors. Additional current costing data was provided by ophthalmic equipment vendors, INNOVA, Topcon, and Ocular Health Network. Costs were converted to 2014 US dollars.[10-14] This research study has no financial relationships, investments, or sponsorship related to the cited commercial vendors.

3.2.5 Data Analysis

Data was synthesized and analyzed using STATA 13. When studies reported estimates as a range or p-value or multiple estimates, mean and standard deviation (SD) were derived. Hierarchical logistic regression was used to determine the pooled estimates of sensitivity and specificity of teleglaucoma, and in-person examination. Hierarchical modeling was used because it is appropriate for mixed models with group-level data.[15] It incorporates both fixed-effects and random-effects models.[16] The dataset of this study consists of both within study variance and between study variance. Thus, hierarchical logistic regression modelling would allow multilevel analysis.[15,16] A graphical representation of the summary estimates was presented in a Hierarchical Summary Receiver Operator Characteristic (HSROC) curve with 95% confidence intervals and 95% prediction regions.

The positive/negative likelihood ratios (LR+/LR-) were calculated using bivariate models to generate estimates of the likelihood of a positive/negative test in a glaucoma/non-glaucoma patient. From this result the diagnostic odds ratio (DOR) was calculated to determine the relative diagnostic effectiveness of teleglaucoma. DOR is the ratio of the odds of a positive screen test in a glaucoma case relative to the odds of a negative screen test in a non-glaucoma case.[17]

Due to the variability of study effectiveness measures, not one article had a complete set of data. Missing data were missing completely at random.[18] The data was missing due to many reasons such as findings were not reported or the study objectives

were different. Missing data were treated as statistically missing and was coded in the dataset accordingly. This means that the missing values did not contribute to any denominator counts or sample size counts. As a result, the missing data was not included in the analysis. Only articles with complete data were included in each analysis. Study heterogeneity was assessed statistically with the calculation of the I-square.

3.3 Results

A total of 45 studies (101,512 participants) were included in this meta-analysis. Table 3.2 and Table 3.3 display the baseline characteristics of each study. Studies were conducted in 14 different countries with representation in each continent. All articles were published between 1999 and 2014. All studies were observational studies, as there were no randomized controlled trials conducted. Three studies contained economic evaluations or cost-effectiveness analysis. Of the 45 studies, 16 compared teleglaucoma to in-person examination. The other 29 studies analyzed teleglaucoma without comparison or used an evaluation of different teleglaucoma equipment. There was minimal variation in study populations; they included either glaucoma patients or patients who were at risk of glaucoma (based on diabetes status, family history of glaucoma, age, or ethnicity). Table 4 displays additional study details on demographics and study methods (glaucoma definition, pupil dilation, and number of field tests examined). Although there was some variation, less than 10% of studies reported these details. The main outcome measures were specificity and sensitivity (Table 3.5). Other

included outcome measures displayed in table 3.5 are: percentage of glaucoma diagnosed, referral rate, and proportion of images with poor quality.

Costing data was given by nine studies and the quality of analysis of costing is displayed in table 3.6. Teleglaucoma costs vary by the capacity of the service and the type and amount of equipment. The current vendor estimate shows that the total costs for standard glaucoma equipment range from 89,703.53 to 123,164.55 US dollars (Table 3.6).[11,12] Additionally, to transfer images and patient test results securely to ophthalmologists electronically, a service exists costing $62.13 US/month.[10,13] This service allows teleglaucoma technicians and ophthalmologists to log-in electronically to attach, send, view, and assess retinal images and patient test results.

There was a wide range of costing data reported in literature. To demonstrate the distribution, the costing data from the literature shows the cost per detected case of glaucoma ranged from $13.03 – 2020.96 US after conversion to US dollars and adjusted for inflation to 2014 costs (Table 3.7).[13] The range represents teleglaucoma with minimal to optimal amount of resources. The lower range is represented by smaller teleglaucoma services with one grader and one diagnostic instrument (tonometer). The higher range represents a larger teleglaucoma service with a few graders, technicians, and nurses, and the full set of ophthalmic instruments outlined in Table 3.1.The mean cost is $1098.67 US for every case of glaucoma detected (n=3) (Table 3.7). The mean cost of teleglaucoma per patient screened was $922.77 US (n=2) (Table 3.7).

Another necessary costing aspect is the ophthalmologist fee for glaucoma consultation. The ophthalmologist may be compensated for each teleglaucoma referral or time spent on teleophthalmology consultations. Compensation varies by states and/or provinces, government legislation, and available private grants. In the United States, *Medicare* and *Medicaid* provide several reimbursement programs for physicians delivering telemedicine consultations.[18,19] In Ontario, Canada, the compensation for the fee-for service model, is $16.00 CAN per ophthalmic referral.[20] The physician liable for teleglaucoma consultations must be a licensed ophthalmologist in both the area of the service and the patient. Physicians must hold liability coverage appropriate to state/provincial laws. In Canada, the *Canadian Medical Protective Association* provides ophthalmologists with liability coverage for teleophthalmology.[21]

Ten studies had complete data to be included for the analysis for teleglaucoma diagnostic accuracy. The summary estimate for sensitivity was 0.833 [95% CI 0.77, 0.88] and specificity was 0.79 [95% CI 0.668, 0.875] for glaucoma screening using optic nerve examinations (Appendix 3). The summary estimates indicate that teleglaucoma correctly detects 83.3% of glaucoma cases and correctly classifies 79% of those without glaucoma as glaucoma-negative. Figure 3 displays each study estimate and the summary estimate with its associated confidence intervals and the generated HSROC curve. The HSROC curve demonstrated a fairly narrow range which indicates that changing the summary specificity moderately affects the summary sensitivity. The HSROC curve was a positive upward slope indicating a positive relationship between specificity and sensitivity; there is a positive trade-off between the two effectiveness

measures. The HSROC curve lies above the threshold, indicating the accuracy of teleglaucoma is better than random chance. The HSROC curve appears in the left upper quadrant and provides a large area under the curve. This is an important measure of accuracy; because the area under the HSROC curve is large, this means teleglaucoma is a relatively accurate screening device.

The distribution of the studies in the HSROC plot demonstrates the variability of both specificity and sensitivity amongst studies. Six studies fall outside of the 95% confidence interval of the summary estimate. The 95% prediction region is the estimate of future observations. The results demonstrate a fairly wide prediction region for both true predictions of specificity and sensitivity, with greater variability expected for specificity.

The study populations used to assess diagnostic accuracy were those at-risk of glaucoma (based on diabetes status, family history, age, ethnicity, etc.), optometrist and ophthalmic clinic patients, and patients who were glaucoma suspects (Table 3.1). One study reported its study population as glaucoma patients only (Table 3.1) and on the contrary, this study had one of the lower reported scores for diagnostic accuracy: specificity was 71.5% and sensitivity was 67% (Table 3.5).[24]

The diagnostic tools of the included studies varied slightly (Table 3.8). Eight out of the ten studies analyzed for sensitivity and specificity used at minimum optic nerve examinations as part of the screening process (Table 3.8). The other two studies reported using IOP or visual field defects as the methods to detect glaucoma suspects

(Table 3.8). For these studies which did not include fundus photographs, the sensitivity and specificity were 81.5% and 95.5% respectively for glaucoma screening using only visual field and 38.1% and 98.8% respectively for glaucoma screening using IOP and Orbscan Topography (Table 3.5).[25,26]

Three studies reported sensitivity and specificity of in-person examination. The weighted mean of sensitivity was 74.9 $\pm$ 27.6% (n=3) and specificity was 88.8 $\pm$ 10.3% (n=3) for in-person examination. The summary estimates indicate that in-person examination correctly detects 74.9% of glaucoma cases and correctly classifies 88.8% of those without glaucoma as glaucoma-negative.

The positive likelihood ratio was 3.97 [95% CI: 2.3-6.7] while the negative likelihood ratio was 0.21 [95% CI: 0.14-0.32] (Appendix 3). This demonstrates that the likelihood of a positive screen test in a glaucoma case is greater than the likelihood of a negative screen test in a non-glaucoma case. In addition, the positive likelihood ratio is greater than one and thus the positive screen test is associated with glaucoma. Since the negative likelihood ratio is less than one, the negative screen test is associated with the absence of the disease.[17] The effectiveness of the diagnostic accuracy of teleglaucoma was given by the DOR, which was 18.7 [95% CI: 7.9-44.4] (Appendix 3). The relative odds of a positive screen test in glaucoma cases are 18.7 times more likely than a negative screen test in a non-glaucoma case. Since the DOR was greater than one, the test is discriminating between true positives and true negatives correctly.[17]

There was insufficient data to conduct hierarchical logistic regression on the percentage of glaucoma diagnosed. Three of the 45 studies reported percentage of glaucoma diagnosed in both teleglaucoma and in-person examination necessary for analysis. The mean percentage of glaucoma diagnosed was 13.4% for teleglaucoma and 7.8% for in-person examination which suggests that teleglaucoma is capable of detecting more cases of glaucoma.

Other effectiveness measures of teleglaucoma were analyzed such as variables of healthcare service quality. The mean percentage of patients referred to a specialist for consultation was 12.5 $\pm$ 7.8% (n=6). The mean percentage of images that were of poor quality was 10.4 $\pm$ 6.7% (n=7). It took a mean time of 75.6 $\pm$ 87.7 seconds (n=4) to process the teleglaucoma images. Timing associated with teleglaucoma service is another measure of quality. The mean time for screening was 8.8 $\pm$ 5.1 minutes (n=3). The time reported for an ophthalmologist to make a diagnosis was 34 minutes (n=1). The mean reporting time was 7.6 $\pm$ 2.6 minutes (n=6). Teleglaucoma gave a reduction for patient travel time of 61.23 hours (n=1). Teleglaucoma had a mean access time (time from patient being referred to the date visit is booked) of 59.7 $\pm$ 9.9 minutes (n=4) in comparison to 73.7 $\pm$ 29.8 minutes (n=4) for in-person examination. The mean cycle time (time from registration until patient leaves clinic) for teleglaucoma was 81.7 $\pm$ 6 minutes (n=2), which was less than that of in-person examination, 116 $\pm$ 2.5 minutes (n=2). The mean proportion of patient satisfaction with teleglaucoma was 47.3 $\pm$ 8.8% (n=2) while only 42% (n=1) were satisfied with in-person examination.

The heterogeneity amongst the studies was given by the I-square. The I-square generated for specificity was 65.2% (p=0.05) and for sensitivity the I-square was 75.6% (p=0.52). This indicates there is moderate heterogeneity (50-75%) between studies regarding the specificity estimates.[27] In addition, the I-square is statistically significant. Thus, the variation between studies is statistically significant. This can bias the pooled estimate for specificity. The I-square for sensitivity falls within the criteria for moderate and substantial heterogeneity (>75% indicates substantial heterogeneity).[19,27] There was substantial variation between studies regarding the sensitivity estimate. However, the heterogeneity was not statistically significant (p>0.05). Thus, although there was heterogeneity reported, it was not statistically significant. Consequently, this means there was potential homogeneity rather than heterogeneity regarding the study estimates for sensitivity.[19] Homogeneity, similarity between studies, is beneficial to the pooled estimate as it indicates a lack of bias.[19]

3.4 Discussion

Telemedicine has demonstrated good use for offering glaucoma services to people of remote areas. Teleglaucoma is beneficial to remote areas as the physician is not required to see patients in person, which reduces wait times and shortens the length of ophthalmic consultations. Teleglaucoma avoids long distance travel and time wasted on commute.

The results of the pooled estimates for diagnostic accuracy have shown teleglaucoma to be less sensitive and more specific than in-person examinations.

Teleglaucoma is advantageous at detecting true positive cases of glaucoma, but has a higher rate of false positives in comparison to in-person examination. However, for teleglaucoma screening it is more important to have a low level of false negatives. This is because if cases of glaucoma are not detected, they are not treated. Without treatment, glaucoma can progress to advanced stages unknowingly. This is significant because as glaucoma progresses vision loss and visual defects become more severe and more importantly, visual impairment due to glaucoma is permanent. Thus, a low level of false negatives can avoid patients missing out on treatment. In addition, with very high DOR estimates, it is suggested that teleglaucoma can accurately discriminate screen tests.

Teleglaucoma has demonstrated capability to detect glaucoma cases that may not have been detected during in-person examination. Glaucoma progresses without patient awareness and it is usually detected at the advanced stages. Thus, teleglaucoma serves as a tool for early detection of glaucoma. If caught earlier and with treatment, glaucoma can be effectively managed and can result in the preservation of vision.

Telemedicine for glaucoma can have several combinations of examinations and measurements used for glaucoma screening. Examination of fundus photographs are commonly used for teleglaucoma screening. Four of the ten studies analyzed used only fundus examinations while another four studies included IOP, CCT, visual field loss, and visual acuity, in addition to fundus photograph examinations (Table 8). Two studies did not use fundus photograph examination, but rather visual acuity, IOP, CCT, and ACT

(Table 8). However, this is based on studies who explicitly stated the terms for ophthalmic examination. Some studies reported “comprehensive eye examinations” were performed, but did not explicitly state which examinations were performed, thus assumptions cannot be made. The use of different tests for glaucoma screening can potentially bias the results as the more diagnostic tools used during screening results in a greater probability of correct diagnosis naturally. However, the results did not show any significant differences in accuracy with studies which reported using multiple diagnostic tools. Interestingly, the specificity and sensitivity values reported ranged independent of the number and the type of examination used for teleglaucoma (Table 4 and Table 8).

The combinations of examinations are dependent on financial and resource limitations of the hosting organization and can vary from small programs to very large programs. It is dependent on the target goals and target populations of the organization. However, the standard examinations recommended for glaucoma screening are those that can evaluate visual field defects, IOP, and the biological structure and function of the optic nerve. These include HRT, OCT, optic disc photography, RNFL photography, as well as FDT, tonometry, and perimetry.[27]

There were limitations within the study. Insufficient data reported was a major limitation of the meta-analysis, although authors were contacted for additional information. Nevertheless, the key goal was to systematically review the literature on tele-glaucoma and in-person screening and perform the meta-analysis. With small sample sizes there was not enough power to show statistical or clinical significance.

Different comparators were reported by studies and to ensure internal validity, only studies with exact comparators were analyzed together. This was one of the reasons for reduced sample sizes for the analysis. However, our analysis does provide information on diagnostic accuracy of teleglaucoma, its capability to detect glaucoma, and to detect negative and positive cases correctly. It demonstrates teleglaucoma has the potential as a screening device to detect a greater amount of cases than in-person examination. Since teleglaucoma is an active screening, it suggests glaucoma cases are detected at earlier stages. However the significance of this difference is limited by the number of comparative studies. The majority of the studies were non-comparative which, in addition, limits the significance of the relative effectiveness to in-person examination.

Teleglaucoma has been evaluated in many different ways: diagnostic accuracy, cost reduction, technological capabilities (image quality, image transmission speed, etc.), reduction of patient and health care provider time, and convenience. Thus many studies focus on part of the effectiveness. As a result, there is insufficient data when summarizing all of the studies together. This has proven the need for more research literature on the diagnostic accuracy of teleglaucoma and its ability to detect glaucoma in comparison to in-person examination. There is a need for research on the follow-up of detected cases and long-term effects of teleglaucoma. In addition, better quality of evidence through randomized controlled trials is recommended. There are implications for cost-effectiveness analyses. Although, costing data suggests cost savings for patients' time and travel with teleglaucoma. Thus, a thorough costing of current health

care expenditure is required to determine its overall cost-effectiveness from the scope of the healthcare system.

Teleglaucoma is beneficial to offering services in underserviced regions and rural areas. It considerably reduces patient access times and cycle times. The time required for service is shorter than in-person examination and physician commitments are reduced. As a result teleglaucoma saves costs to patients and costs to the health care system as a whole.

3.5 Literature Cited

1. Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 90(3): 262–267.

2. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

3. Lalkhen AG, McCluskey A. (2008) Clinical tests: sensitivity and specificity. Cont Educ Anaesth Crit Care Pain. 8:221-223.

4. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J et al. (2011) GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J Clin Epidemiol 64:407–415.

5. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R et al. (2011) GRADE guidelines: 5. Rating the quality of evidence-publication bias. J Clin Epidemiol 64:1277–1282.

6. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P et al. (2011) GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol 64:1283–1293.

7. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J et al. (2011) GRADE guidelines: 7. Rating the quality of evidence-inconsistency. J Clin Epidemiol 64:1294–1302.

8. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J et al. (2011) GRADE guidelines: 8. Rating the quality of evidence-indirectness. J Clin Epidemiol 64:1303–1310.

9. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA et al. (2011) GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 64:1311–1316.

10. Bank of Canada. (2014) Daily Currency Converter. Available: http://www.bankofcanada.ca/rates/exchange/daily-converter/.

11. INNOVA Medical Ophthalmics. Vendor Quotation Oct. 8, 2014. Ontario, Canada.

12. Topcon Canada Inc. Vendor Quotation Oct. 23, 2014. Ontario, Canada.

13. Ocular Health Network. Vendor Quotation Oct. 14, 2014. Ontario, Canada.

14. Bank of America. Foreign Currency Exchange. Available: https://www.bankofamerica.com/foreignexchange/currency-converter.go 2014 July 25. Accessed 2014 July 25.

15. Rutter CM, Gatsonis CA. (2001) A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med. 2001 Oct 15;20(19):2865-84. Available: http://www.ncbi.nlm.nih.gov/pubmed/11568945

16. Wong G, Mason W. (1985) The Hierarchical Logistic Regression Model for Multilevel Analysis. J Amer Stat Assoc. Vol. 80, No. 391 (Sep., 1985), pp. 513-524. Published by: Taylor & Francis, Ltd. on behalf of the American Statistical Association. Available: http://www.jstor.org/stable/2288464

17. Trikalinos T, Balion C, Coleman C et al. (2012) Meta-analysis of test performance when there is a “gold standard.” AHRQ Publication No. 12-EHC080-EF. Chapter 8 of Methods Guide for Medical Test Reviews (AHRQ Publication No. 12-EHC017). Rockville, MD: Agency for Healthcare Research and Quality.

18. Agostino R, Sulllivan L, Beiser A. (2006) Introductory Applied Statistics. Brooks/Cole Cengage.

19. Guyatt G, Rennie D, Meade M, et al. (2008) Users' Guides to the Medical Literature: essentials of Evidence-Based Clinical Practice. 2nd edition (Jama & Archives Journals). McGraw-Hill. Professional.

20. Centers for Medicare & Medicaid Services (2014) Telehealth Services. American Medical Association ICN 901705. Available: http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/TelehealthSrvcsfctsht.pdf Accessed 2014 Oct. 19.

21. Centers for Medicare & Medicaid (2014) Medicare Benefit Policy Manual, Chapter 15: Covered Medical and Other Health Services. Department of Health of Human Services, Publication # 100-04. Available: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf Accessed 2014 Oct. 19.

22. Toronto Central Local Health Integration Networks (LHIN) (2014) Teleophthalmology Services. Available: http://www.torontodiabetesreferral.com/teleophthalmology-service Accessed 2014 Oct. 19.

23. Ng M, Nathoo N, Rudnisky C et al. (2009) Improving Access to Eye Care: Teleophthalmology in Alberta, Canada. J Diabetes Sci Technol 3(2): 289-296.

24. Eikelboom RH, Yogesan K, Constable IJ et al. (1999) A handheld CCD fundus camera: an alternative to retinal photographs for glaucoma screening and telemedicine? Invest Ophthalmol Vis Sci 40(4MA 3488B346).

25. Ianchulev T, Pham P, Makarov V et al. (2005) Peristat: a computer-based perimetry self-test for cost-effective population screening of glaucoma. Curr Eye Res 30(1): 1-6.

26. Kumar S, Middlemiss C, Bulsara M et al. (2006) Telemedicine-friendly, portable tonometers: an evaluation for intraocular pressure screening. J Clin Exp Ophthalmol Sep-Oct; 34(7):666-70.

27. Higgins J, Green S. (2011) The Cochrane Handbook for Systematic Reviews of Interventions. Chapter 9 Analysing data and undertaking meta-analyses. [Accessed 2015-July-4] Available: http://handbook.cochrane.org/chapter_9/9_analysing_data_and_undertaking_meta_analyses.htm

28. Moyer VA and U.S. Preventive Services Task Force (2013) Screening for Glaucoma: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 159:484-489.

29. Tuulonen A, Ohinmaa A, Alanko H et al (1999) The application of teleophthalmology in examining patients with glaucoma: a pilot study. J Glaucoma 8:367-73.

30. Li HK, Tang RA, Oschner K et al. (1999) Telemedicine screening of glaucoma. American Telemedicine Association. Telemed J 5(3): 283-90.

31. Yogesan K, Constable IJ, Barry CJ et al. (1999) Evaluation of a portable fundus camera for use in the teleophthalmologic diagnosis of glaucoma. J Glaucoma 8(5): 297-301.

32. Michelson G, Striebel W, Prioda W et al. (2000) Telemedicine in the control of intra-ocular pressure. J Telemed Telecare 6 Suppl 1: S126-8.

33. Yogesan K, Constable IJ, Morgan W et al. (2000) International transmission of tele-ophthalmology images. J Telemed Telecare 6(1): 41-4.

34. Yogesan K, Cuypers M, Barry CJ et al. (2000) Tele-ophthalmology screening for retinal and anterior segment diseases. J Telemed Telecare 6 Suppl 1: S96-8.

35. Gonzalez F, Iglesias R, Suarez A et al. (2001) Teleophthalmology link between a primary health care centre and a reference hospital. Med Inform Internet Med 26(4): 251-63.

36. Sebastian MA, Ayala ME, Sobas EM et al. (2001) Assessment of a telemedicine screening program for glaucoma in a Spanish population. Invest Ophthalmol Vis Sci 42(4SU SMA 2994).

37. Wegner A, Zahlmann G (2003) Internet Based Glaucoma Screening. ARVO Meeting Abstracts. 44(5): 3417.

38. Labiris G, Fanariotis M, Christoulakis C et al. (2003) Tele-ophthalmology and conventional ophthalmology using a mobile medical unit in remote Greece. J Telemed Telecare 9(5): 296-9.

39. Fansi A, Harasymowycz P, Descovich D et al (2003) Using HRT for telemedicine in glaucoma screening: The effect of different image file format on diagnosis of glaucoma. Invest Ophthalmol Vis Sci 44SU 2MA 3379.

40. Jin AJ, Martin D, Maberley D et al. (2004) Evaluation of a mobile diabetes care telemedicine clinic serving Aboriginal communities in Northern British Columbia, Canada. Int J Circumpolar Health 63 Suppl 2: 124-8.

41. Chen L, Tsai C, Liu T et al. (2004) Feasibility of tele-ophthalmology for screening for eye disease in remote communities. J Telemed Telecare 10(6): 337-341.

42. de Mul M, de Bont AA, Reus NJ et al. (2004) Improving the quality of eye care with tele-ophthalmology: shared-care glaucoma screening. J Telemed Telecare 10(6): 331-6.

43. Paul PG, Raman R, Rani PK et al. (2006) Patient satisfaction levels during teleophthalmology consultation in rural south India. Telemed J E-Health. 12(5):571-8

44. Kumar S, Giubilato A, Morgan W et al. (2007) Glaucoma screening: analysis of conventional and telemedicine-friendly devices. J Clin Exp Ophthalmol 35(3): 237-43.

45. Khouri AS, Szirth BC, Salti HI et al. (2007) DICOM transmission of simultaneous stereoscopic images of the optic nerve in patients with glaucoma. J Telemed Telecare 13(7): 337-340.

46. Pasquale LR, Asefzadeh B, Dunphy RW et al. (2007) Detection of glaucoma-like optic discs in a diabetes teleretinal program. Optometry 78(12):657–63.

47. Khouri A, Szirth B, Shahid K et al. (2008) Software-assisted optic nerve assessment for glaucoma tele-screening. Telemed J E-Health. 14(3): 261-5.

48. de Bont A, Bal R (2008) Telemedicine in interdisciplinary work practices: On an IT system that met the criteria for success set out by its sponsors, yet failed to become part of every-day clinical routines. BMC Med Inform Decis Mak 8AR 47

49. Sogbesan E, Rudnisky C, Tennant M et al. (2010) Time and cost-benefit analysis of a collaborative web-based stereoscopic teleglaucoma care model. Canadian Ophthalmology Society Annual Meeting.

50. Anton-Lopez A, Cots M, Duran-Tauleri F (2011) Cost-Effectiveness Analysis of a Telemedicine Program for the Detection of Glaucoma with Imaging Devices. ARVO Annual Meeting Abstract Search and Program Planner 2011: 251.

51. Khurana M, Ramakrishnan R, Kader M (2011) Teleophthalmology aided Vision Centres in Rural South India: Role and Utilization of Services. ARVO Annual Meeting Abstract Search and Program Planner 2011: 4228.

52. Staffieri SE, Ruddle JB, Kearns LS, et al. (2011) Telemedicine model to prevent blindness from familial glaucoma. Clin Experiment Ophthalmol 39(8):760-5.

53. Swierk T, Jurgens C, Grossjohann R, et al. (2011) Health economical aspects of telemedical glaucoma monitoring. Ophthalmologe 108(4):342-50.

54. Amin S, Damji K, Kassam F, et al. (2012) In-house patient-centered teleglaucoma improves access and efficiency for glaucoma suspects and those with early stages of open-angle glaucoma (OAG). Canadian Ophthalmology Society Annual Meeting.

55. Shahid K, Kolomeyer A, Nayak N, et al. (2012) Ocular telehealth screenings in an urban community. American Telemedicine Association. Telemed J E-Health 18(2): 95-100.

56. Kassam F, Amin S, Sogbesan E, Damji K (2012) The use of teleglaucoma at the University of Alberta. J Telemed Telecare 8:367.

57. Gupta S, Sinha SK, Dagar AB (2013) Evaluation of the effectiveness of diagnostic & management decision by teleophthalmology using indigenous equipment in comparison with in-clinic assessment of patients. Indian J Med Res 138:531-5.

58. Damji K, Arora S, Rudnisky C (2013) Improving access and cycle time through a hospital based teleglaucoma program. Canadian Ophthalmological Society Annual Meeting.

59. Kiage D, Kherani I, Gichuhi S, Damji K, Nyenza M (2013) The Muranga Teleophthalmology Study: Comparison of Virtual (Teleglaucoma) with in-person clinical assessment to diagnose glaucoma. Middle East Afr J Ophthalmol 20(2): 150-157.

60. Verma S, Arora S, Kassam F, Edwards M, Damji K (2013) Tele-glaucoma clinical outcomes and referral pathway. Canadian Ophthalmological Society Annual Meeting.

61. Ahmed R, Petrany S, Fry R, Krasnow M (2013) Screening diabetic and hypertensive patients for ocular pathology using telemedicine technology in rural West Virginia: a retrospective chart review. W V Med J 109(1): 6-10.

62. Arora S, Rudnisky C, Damji K (2014) Improved Access and Cycle Time with an “In-house” patient-centered teleglaucoma program versus traditional in-person assessment. Telemed J E-Health 20(5):439-45.

3.6 Tables

Table 3.1: Standardized Teleglaucoma Equipment

Components	**Requirements**
Human Resources	Staff: graders, Ophthalmic technicians, nurses, optometrist, physicians, glaucoma specialists/ophthalmologists
Information Technology	Secure Diagnostic Imaging (SDI) system Videoconferencing equipment Computer systems and software ISDN installation
Screening Equipment	Retinal camera Tonometer Devices to measure central corneal thickness Frequency Doubling Technology (FDT) or Humphrey Visual Field test Optical Coherence Tomography Slit lamp Gonioscope Retinal camera Tonometer Devices to measure central corneal thickness
Examinations	Medical & family history Visual acuity IOP CCT Pupil equal and reactive to light (PERL) or relative afferent pupillary defect (RAPD) Slit lamp Gonioscopy Visual field Fundus photographs OCT

	Ancillary tests

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.2: Baseline Characteristics of Included Studies - Demographics

Author (Year)	Location	Study Design	Sample Size	Population
Tuulonen et al. (1999)[23]	Finland	PC	70	Glaucoma patients
Eikelboom et al. (1999)[19]	Australia	PC	27	Glaucoma patients
Li et al. (1999)[24]	USA	PC	32	Diabetic adults
Yogesan et al. (1999)[25]	Australia	PC	27	Glaucoma clinic patients/suspected of glaucoma
Michelson et al. (2000)[26]	Germany	PC	10	Glaucoma-diagnosed patients
Yogesan et al. (2000)[27]	Indonesia	PC	14	Ophthalmic Clinic patients
Yogesan et al. (2000)[28]	Australia	PC	43	Ophthalmic Clinic patients
Gonzalez et al. (2001)[29]	Spain	PC	139	Ophthalmic Clinic patients
Sebastian et al. (2001)[30]	Spain	CS	74	Glaucoma suspects
Wegner et al. (2003)[31]	Germany	PC	1733	Not stated
Labiris et al. (2003)[32]	Greece	PC	1205	Glaucoma-diagnosed patients
Fansi et al. (2003)[33]	Canada	PC	33	Glaucoma suspects or diagnosed
Jin et al. (2003)[34]	Canada	CEA	339	Diabetic aboriginals
Chen et al. (2004)[35]	Taiwan	PC	113	Residents of area aged > 40 years
de Mul et al. (2004)[36]	Netherlands	PC	1729	Optometrist patients at-risk for glaucoma
Ianchulev et al. (2005)[20]	USA	PC	33	Glaucoma suspects or diagnosed
Paul et al. (2006)[37]	India	PC	348	Rural residents at risk for glaucoma
Kumar et al. (2006)[21]	Australia	PC	107	Patients of the Eye Clinic
Kumar et al. (2007)[38]	New Zealand	PC	201	General eye examination clinic Patients
Khouri et al. (2007)[39]	Not Stated	CS	30	Glaucoma-diagnosed patients
Pasquale et al. (2007)[40]	USA	PC	350	Diabetic
Khouri et al. (2008)[41]	USA	PC	28	Glaucoma-diagnosed patients

deBont et al. (2008)[42]	USA	PC	1729	Optometrist patients at-risk for glaucoma
Sogbesan et al. (2010)[43]	Canada	CEA/PC	--	Optometrist patients at-risk for glaucoma
Anton-Lopez et al. (2011)[44]	Spain	CS	1599	At-risk for glaucoma
Khurana et al. (2011)[45]	India	CS	91698	Ophthalmic Clinic patients
Staffieri et al. (2011)[46]	Tasmania	PC	133	High risk (First degree relatives of diagnosed POAG)
Swierk et al. (2011)[47]	Germany	EE	--	Ophthalmic Clinic patients
Amin et al. (2012)[48]	Canada	PC	72	Glaucoma suspects or early stages of OAG
Shahid et al. (2012)[49]	USA	CS	341	Urban soup kitchen/homeless
Kassam et al. (2012)[50]	Canada	PC	257	At-risk for glaucoma or early-stage glaucoma
Gupta et al. (2013)[51]	India	PC	247	Ophthalmic Clinic patients
Damji et al. (2013)[52]	Canada	PC	71	Ophthalmic Clinic patients
Kiage et al. (2013)[53]	rural Africa	PC	309	Diabetic adults
Verma et al. (2013)[54]	Canada	RC	247	Optometrist-referred glaucoma suspects or early OAG
Ahmed et al. (2013)[55]	USA	RC	643	Diabetic and hypertensive
Arora et al. (2014)[56]	Alberta	PC	71	Glaucoma clinic patients/suspected of glaucoma
Legend: CS = Cross-Sectional Study, PC = Prospective Cohort Study, CEA = Cost-effectiveness Analysis, RCS = Retrospective Cohort Study, EE = Economic Evaluation, -- = Not Stated				

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.3: Baseline Characteristics of Included Studies - Intervention

Author (Year)	Teleglaucoma Equipment	Comparator
Tuulonen et al. (1999)[23]	Canon CR5-45NM non-mydriatic fundus camera, slit-lamp, Panasonic video camera, HF II perimeter	In-person examination
Eikelboom et al. (1999)[19]	Nidek Nm-100 Handheld fundus camera	Teleglaucoma only
Li et al. (1999)[24]	Non-mydriatic retinal camera. Digital images	Image Quality of Teleglaucoma
Yogesan et al. (1999)[27]	Portable fundus camera, Nidek NM100	Teleglaucoma only
Michelson et al. (2000)[26]	Self-tonometry portable device called Ocuton, PalPilot, IOP curve	Teleglaucoma only
Yogesan et al. (2000)[27]	Handheld fundus camera (NM100)	Teleglaucoma only
Yogesan et al. (2000)[28]	DIO digital indirect ophthalmoscope, handheld fundus camera Nidek NM100, stereo fundus camera (Nidek 3D-x)	Teleglaucoma only
Gonzalez et al. (2001)[29]	Non-mydriatic fundus camera (canon CR6-45M)	In-person examination
Sebastian et al. (2001)[30]	C-20-5 FDT, Humphrey-Zeiss, & Topcon optic nerve head photographs	Teleglaucoma only
Wegner et al. (2003)[31]	Goldman applanation tonometer and mobile HRT	Teleglaucoma only
Labiris et al. (2003)[32]	Slit lamp, Octapus perimeter visual field, fundus camera, Optotype, air tonometer	In-person examination
Fansi et al. (2003)[33]	--	Healthy vs Glaucoma eyes
Jin et al. (2003)[34]	Tonometry	In-person examination
Chen et al. (2004)[35]	Digital 35-degree colour fundus images, non-mydriatic digital fundus camera (CR6-45, Canon)	In-person examination
de Mul et al. (2004)[36]	Nerve fibre analyser, GDx	In-person examination
Ianchulev et al. (2005)[20]	Peristat: self-test	In-person examination
Paul et al. (2006)[37]	--	Teleglaucoma only
Kumar et al. (2006)[21]	I-care tonometry	Teleglaucoma only
Kumar et al. (2007)[38]	--	In-person examination
Khouri et al. (2007)[39]	Digital stereo fundus camera - Nidek 3-Dx	Image Quality of Teleglaucoma
Pasquale et al.	Topcon TRC NW-5S non-mydriatic retinal camera	Teleglaucoma

Author (Year)	Teleglaucoma Equipment	Comparator
(2007)[40]	(Paramus) interfaced to a standard color video camera (Sony 970-MD)	only
Khouri et al. (2008)[41]	Non-mydriatic 45-deg camera, Canon Japan. DICOM image format	Image Quality of Teleglaucoma
deBont et al. (2008)[42]	Nerve fibre analyser, GDx	Image Quality of Teleglaucoma
Sogbesan (2010)[43]	--	In-person examination
Anton-Lopez et al. (2011)[44]	HRT, nerve-fibre analyzer (GDX-VCC), I-Care (rebound tonometry)	In-person examination
Khurana et al. (2011)[45]	--	Teleglaucoma only
Staffieri et al. (2011)[46]	--	Teleglaucoma only
Swierk et al. (2011)[47]	--	In-person examination
Amin et al. (2012)[48]	Slit lamp, IOP, CCT, visual field, anterior and stereo posterior segment photos and OCT	In-person examination
Shahid et al. (2012)[49]	8.2 megapixel non-mydriatic retinal camera	Teleglaucoma only
Kassam et al. (2012)[50]	Remote service - slit lamp, fundus photographs,	In-person examination
Gupta et al. (2013)[51]	Fundus Camera (Portcam II)	In-person examination
Damji et al. (2013)[52]	--	In-person examination
Kiage et al. (2013)[53]	Topcon 777	In-person examination
Verma et al. (2013)[54]	--	In-person examination
Ahmed et al. (2013)[55]	Topcon TRC non-mydriatic retinal camera, Tonopen	Teleglaucoma only
Arora et al. (2014)[56]	--	In-person examination

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.4: Additional Details on Baseline Characteristics of Included Studies

Author (Year)	Study Population Ethnicity	Glaucoma definition	Dilated pupil	# Field tests
Eikelboom et al. (1999)[19]	– –	– –	Yes	– –
Yogesan et al. (1999)[25]	– –	– –	Yes	– –
Yogesan et al. (2000)[27]	– –	– –	Yes	– –
Yogesan et al. (2000)[28]	– –	– –	Yes	– –
Ianchulev et al. (2005)[20]	15% White, 9% African American, 76% Hispanic	– –	No	– –
Chen et al. (2004)[35]	100% Asian	"The diagnosis of glaucoma was made according to the anatomical findings from the patient's optic nerve disc, and functional visual field examination by frequency-doubling perimetry (FDP). Intraocular pressure (IOP) was also evaluated. An elevated IOP was defined as over 17mmHg (1mmH = 133 Pa). Severe glaucoma was defined as an optic cup: disc ratio over 0.7 with an FDP defect or elevated IOP. Mild glaucoma was defined as an optic cup: disc ratio between 0.7 and 0.5, or disc asymmetry of over 20%, with an FDP defect or elevated IOP."	– –	– –
Kumar et al. (2006)[21]	96% Caucasian, 4% Asian	IOP of 21 mmHg was threshold for suspected glaucoma	– –	– –
Paul et al. (2006)[37]	100% Indian	– –	– –	– –
Kumar et al.	– –	In accordance with glaucoma screening protocol of Lions Eye	Yes	– –

Author (Year)	Study Population Ethnicity	Glaucoma definition	Dilated pupil	# Field tests
(2007)[38]		Institute: Vertical cup disc ratio (VCDR) >0.5, IOP>21 mmHg, abnormal visual field related to glaucoma, and or disk asymmetry >0.2.		
Pasquale et al. (2007)[40]	16% African American (of glaucoma suspects) 14% African American (Of non-glaucoma suspects)	“VFs were considered glaucomatous if the pattern deviation plot showed a nasal step, nasal depression, arcuate defect, paracentral loss that respected the horizontal meridian, or temporal wedge defects based on previously published criteria... Patients were designated as “no glaucoma” if the CDR was "<0.6 in both eyes and CDR asymmetry was < 0.1 in the absence of reliable glaucomatous VFs. Patients were designated as having “glaucoma-suspicious optic discs” if the CDR was "> 0.6 in either eye or CDR asymmetry was > 0.1 with or without reliable glaucomatous VFs. Patients with more subtle optic nerve changes were labeled as having glaucoma-suspicious optic discs if VFs were available and reliable and showed change consistent with glaucomatous loss."	– –	Three
Staffieri et al. (2011)[46]	– –	"Subjects were classified as having definite glaucoma on the basis of characteristic optic nerve head changes (cup: disc ratio [CDR] outside the 97.5 percentile for the normal population or rim width less than 0.1 CDR at the superior and inferior poles of the disc) and definite visual field defect consistent with glaucoma. Individuals with stereoscopic disc photos consistent with structural damage but in whom field testing was unreliable or unobtainable were classified as glaucoma suspect."	Yes	– –

Author (Year)	Study Population Ethnicity	Glaucoma definition	Dilated pupil	# Field tests
Khurana et al. (2011)[45]	100% Indian	– –	– –	– –
Anton-Lopez et al. (2011)[44]	– –	"2/3 Criteria were considered suspects and referred for glaucoma consultation: (1) global Moorefield's Regression Analysis borderline or outside normal limits, (2) Nerve Fibre Index >30, and tonometry >21mmHg."	– –	– –
Shahid et al. (2012)[49]	78% African American, 10% Caucasian, 6.7% Hispanic, 4.8% Other	– –	Yes	One
Kiage et al. (2013)[53]	100% African	Category 1 diagnosis (structural and functional evidence): 2 out of 3 of the following: VCDR $\geq$0.7, focal glaucoma disc changes, VCDR asymmetry ($\geq$ 0.2). Category 2 diagnosis (structural evidence with unproved field loss): 2 out of 3 of the following: VCDR $\geq$0.8, focal glaucoma disc changes, VCDR asymmetry $\geq$ 0.3. Category 3 diagnosis (optic disc not clearly seen): 1 of the following visual acuity < 3/60 and IOP > 21 mmHg or visual acuity < 3/60 and evidence of glaucoma surgery or medical records confirming glaucoma morbidity. Glaucoma suspect: one of the following IOP $\geq$ 23 mmHg, 1/3 of the glaucomatous optic neuropathy listed in category 2, glaucoma visual field defect only.	Yes	Three
Gupta et al. (2013)[51]	100% Indian	Glaucoma diagnosis based on disc findings VCDR of $\geq$ 0.7 or focal neuroretinal rim defect.	Yes	– –

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.5: Study Relevant Outcome Measures

Author (Year)	Specificity (%)	Sensitivity (%)	Percentage Glaucoma diagnosed	Percentage Referral Rate	Percentage of Image of Poor Quality
Li et al. (1999)[24]	– –	– –	– –	– –	18.8
Yogesan et al. (1999)[25]	84.5	82.5	– –	– –	– –
Eikelboom et al. (1999)[19]	71.5	67	– –	– –	– –
Yogesan et al. (2000)[28]	87	100	– –	– –	– –
Gonzalez et al.(2001)[29]	– –	– –	7.9	– –	13
Sebastian et al. (2001)[30]	– –	– –	2.7	– –	4
Wegner et al. (2003)[31]	– –	– –		– –	9.4
de Mul et al. (2004)[36]	58	82	4.6	11	– –
Ianchulev et al. (2005)[20]	95.5	81.5	– –	– –	– –
Kumar et al. (2006)[21]	98.8	38.1	– –	– –	– –
Kumar et al. (2007)[38]	93.6	91.1	– –	– –	– –
Pasquale et al. (2007)[40]	96	59	– –	– –	– –
deBont et al. (2008)[42]	– –	– –	– –	11	11
Staffieri et al. (2011)[46]	– –	– –	5	– –	– –

Anton-Lopez et al. (2011)[44]	– –	– –	1.9	7.7	– –
Khurana et al. (2011)[45]	– –	– –	1.06	12.5	– –
Shahid et al. (2012)[49]	– –	– –	32		– –
Ahmed et al. (2013)[55]	– –	– –	– –	19.4	5
Gupta et al. (2013)[51]	81.82	72.1	– –	– –	– –
Kiage et al. (2013)[53]	89.6	41.3	14	– –	24
Verma et al. (2013)[54]	– –	– –	31	31	
Arora et al. (2014)[56]	– –	– –	44	– –	– –

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.6: Quality of Analysis for Costing

Author (Year)	Object	Costs ($)	Currency
Tuulonen et al. (1999)[23]	<u>Fixed Costs</u>		
	Fundus camera (1 unit)	200	FIM
	ISDN installation (3 units)	6.5	FIM
	Server computer (2 units for 5 years)	50	FIM
	Software application (2 units for 5yrs)	50	FIM
	Video slit-lamp (1 unit)	40	FIM
	Write off 10 years (3%)	40.62	FIM
	Use of teleophthalmology equipment	24.372	FIM
	Video conference equipment	84	FIM
	Write-off 5 years	18.342	FIM
	Automated perimetry – Humphrey	132	FIM
	Write off 10 years (3%)	15.474	FIM
	<u>Other fixed costs</u>		
	Service and updating	5	FIM
	Line costs per month	3.672	FIM
	Premise	1.608	FIM
	Utilities	1.608	FIM
	Other costs	7.133	FIM
Yogesan et al.	Satellite phone	30000	EUR

Author (Year)	Object	Costs ($)	Currency
(2000)[27]			
	Mobile phone	3250	EUR
Jin et al.			
(2003)[34]	Total expenditure capital	160260	CAN
	Operating costs per 1 year	348665	CAN
	Projected 2005 Costs	385226	CAN
	Operating costs amortized over 5 years	32052	CAN
	Operating costs amortized over 5 years per diabetic case	1231	CAN
	Professional and Lab Fees	291	CAN
	Costs per patient	1231	CAN
	Travel costs	805	CAN
	Escort travel expenses	340	CAN
Chen et al.			
(2004)[35]	Costs per detected case	10	US
Ianchulev et al. (2005)[20]	Costs per targeted glaucoma screening	60	US
	Costs per detected case	1000	US
Sogbesan			
(2010)[43]	Patient savings	2527	CAN
Anton-Lopez et al. (2011)[44]	Incremental Costs	24150	EUR
	Costs per detected case	1420	EUR

Author (Year)	Object	Costs ($)	Currency
	Primary Care visit	15	EUR
	General Ophthalmic Visit	18	EUR
	Ophthalmic Visit with tests	52	EUR
	Glaucoma Consultation	26	EUR
Swierk et al. (2011)[47]	Medical Care	291.21	EUR
	Accommodation costs	280	EUR
	Costs per patient	288.72	EUR
Ahmed et al. (2013)[55]	Equipment costs (digital retinal camera, Tonopen and computer)	46000	US
Vendor Estimates (2014)[10, 11]	OCT	48,000 – 49,000	CAN
	Slit Lamp	7,420 - 19,990	CAN
	<u>Tonometer</u>		
	Slit lamp mounted	1,400 – 2,400	CAN
	Non-contact	8,995	CAN
	Retinal Camera	27,900 – 27, 995	CAN
	Visual Field Analyser	16,340 – 32,420	CAN

Author (Year)	Object	Costs ($)	Currency
	TOTAL RANGE:	**89,703.53 - 123,164.55**	US
Ocular Health Network (2014)[12]	Imaging Transfer Service	70/Month	CAN

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.7: Teleglaucoma Estimated 2014 Unit Costs

Author (Year)	Cost per detected case ($US) (Adjusted for inflation to 2014 costs)	Inflation Rate (%)	Cost per patient ($US) (Adjusted for inflation to 2014 costs)	Inflation Rate (%)
Jin et al. (2003)[34]	– –	– –	1434.63	25.49
Chen et al. (2004)[35]	13.03	30.32	– –	– –
Ianchulev et al. (2005)[20]	1262.02	26.2	– –	– –
Anton-Lopez et al. (2011)[44]	2020.96	5.89	– –	– –
Swierk et al. (2011)[47]	– –	– –	410.91	5.89
Mean costs	**1098.67**		**922.77**	

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Table 3.8: Study Ophthalmic Examinations

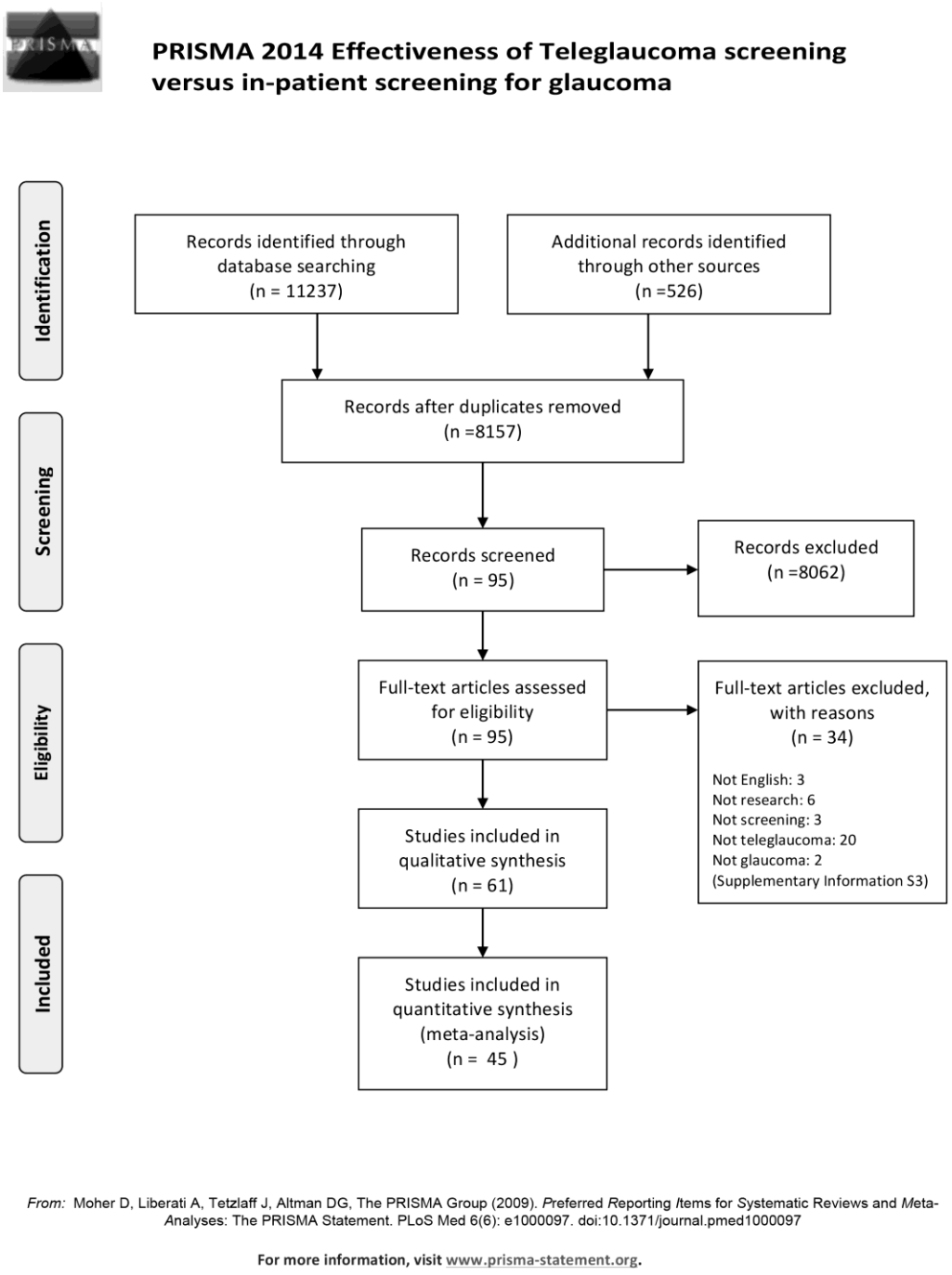
Author (Year)	Examination tests
Li et al. (1999)[24]	Optic disc photographs, VCDR
Yogesan et al. (1999)[25]	VCDR
Eikelboom et al. (1999)[19]	VCDR
Yogesan et al. (2000)[28]	Fundus images, H/VCDR, radial rim measurements
Gonzalez et al.(2001)[29]	Fundus images
Sebastian et al. (2001)[30]	Visual acuity, IOP, FDT, optic nerve head photographs
Wegner et al. (2003)[31]	HRT, IOP, OCT
de Mul et al. (2004)[36]	IOP, nerve fibre indicators
Ianchulev et al. (2005)[20]	HVF, visual acuity
Kumar et al. (2006)[21]	IOP, CCT, ACT
Kumar et al. (2007)[38]	IOP, FDT, VCDR, disc asymmetry, visual field, fundus photographs
Pasquale et al. (2007)[40]	IOP, CDR, Humphrey visual field, comprehensive eye examination
deBont et al. (2008)[42]	Nerve fiber indicators, fundus photographs, IOP
Staffieri et al. (2011)[46]	Visual acuity, refractive status, visual field testing, IOP, CCT, stereoscopic optic disc photographs
Anton-Lopez et al. (2011)[44]	IOP, HRT, nerve fibre indicators
Khurana et al. (2011)[45]	--
Shahid et al. (2012)[49]	IOP, optic nerve head appearance and asymmetry, nerve fibre layer dropouts
Ahmed et al. (2013)[55]	Fundus images, CDR, IOP
Gupta et al. (2013)[51]	Fundus photographs

Kiage et al. (2013)[53]	Slit lamp examination, focal glaucoma damage, VCDR, IOP, FDT, fundus images, visual fields
Verma et al. (2013)[54]	Stereoscopic optic nerve images, visual fields, ancillary tests, IOP, OCT, and HRT
Arora et al. (2014)[56]	OCT, HRT, stereo-nerve photographs, FDT, HVF, OCT, IOP
Legend: VCDR= vertical cup-to-disc ratio, HCDR= horizontal cup-to-disc ratio, IOP= intraocular pressure, FDT= frequency doubling technology, CCT= central corneal thickness, HRT= Heidelberg Retinal Tomography, CDR=cup-to-disc ratio, HVF= Humphrey Visual Field, ACT= anterior chamber depth, POAG= primary open angle glaucoma, OAG= open angle glaucoma	

Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

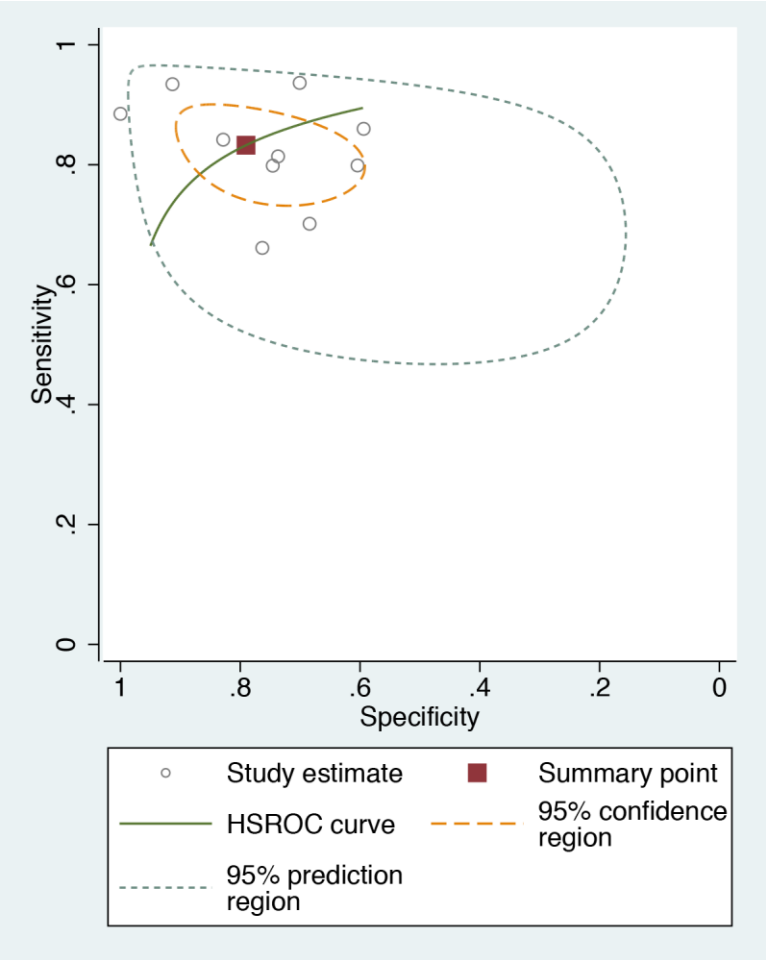
3.7 Figures

Figure 3.1: PRISMA Diagram



Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Figure 3.2: HSROC Curve



Footnote: Thomas S-M, Jeyaraman M, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi:10.1371/journal.pone.0113779

Chapter 4 The cost-effectiveness of teleglaucoma versus in-person examination

4.1 Introduction

The burden of vision loss on the Canadian economy is $15.8 billion per year in which 55% is allocated to direct health care costs.[1] Sixty-five per cent of adults with partial or full vision loss are unemployed, which translates to $4.06 CAN billion annually of lost earnings.[1] In the United States, vision loss costs over $35 billion for direct costs and loss of productivity.[2] Glaucoma is the major eye disease leading to irreversible vision loss. The economic burden of glaucoma alone on the American economy is $2.9 billion.[2]

Screening for glaucoma is important. Glaucoma is a public health concern. It has a prolonged asymptomatic phase and if detected early and with effective therapy blindness can be prevented.[3] Screening has shown to be effective specifically in high-risk populations such as patients older than 50 years and black populations.[3,4] Currently, screening for glaucoma occurs passively within routine ocular examination at the optometrist and/or ophthalmologist clinics. This is referred to as “in-person examination.”[5,6] “Passive” screening is when the patients come to the doctor and “active screening” is when the healthcare providers actively draw patients in for screening. Active screening on a population base, where health care providers provide outreach programs to draw patients in for screening, rarely occurs.[5] Mainly research or community groups conduct population-based screening sporadically and there is no mandated active screening that occurs at a population level.[5] There are two main obstacles with population-based screening: firstly, there is a lack of an efficient screening test and secondly, there is insufficient economic evidence.[5]

Teleglaucoma is an innovative screening test that has the potential to be a sufficient screening tool. Chapter three of this thesis discussed the effectiveness of teleglaucoma and found implementation of teleglaucoma improved the detection of glaucoma on a population level. It was reported by Tuulonen et al that patients were satisfied with teleglaucoma service as it successfully reduced patient costs by 92%, saved patient time by 92%, and there was a 97% reduction in patient travel.[7] A recent study by Thomas et al synthesized the effectiveness of teleglaucoma and found teleglaucoma was effective at screening negative cases.[8] The technology gave poor quality images in only 10.4% of images.[8] It improved access to ophthalmologist and had a referral rate of 12.5% to the ophthalmologist.[8] This chapter will discuss the economic evidence of teleglaucoma's effectiveness and the objective is to determine the cost-effectiveness of teleglaucoma as a screening device for glaucoma in comparison to in-person examination.

Vision impairment associated with glaucoma negatively affects one's Health-Related Quality of life (HRQoL). Preference-based HRQoL is referred to as the individual's perception of his/her disease state and its effect on his/her quality of life.[9] HRQoL can be quantified using utility values which range from 0 indicating death to 1 indicating excellent health with complete functioning.[9] Therefore, glaucoma patients are hypothesized to have a lower utility value and HRQoL than healthy people.

For cost-effectiveness analysis it is necessary to translate effect data into Quality Adjusted life Years (QALYs) to allow easy comparison between different

interventions. QALY incorporates both quality and quantity of life, specifically life expectancy and quality of remaining life years.[9,10] QALYs are the amount of years in a person's life that is adjusted to represent remaining life years in perfect quality.[9,10] It weighs the time spent in different health states. Consequently, teleglaucoma has shown increased ability to detect glaucoma in rural Alberta, allowing for treatment of cases in remote areas that would have not necessarily be treated. In addition, it allows early detection of glaucoma to delay the progression of disease. Thus, it is suggested that teleglaucoma increases patients' utility values, improves their HRQoL, and provides more QALYs compared to standard in-person care.[8]

With implementation of any new technology and service comes an additional cost. Thomas et al reported that teleglaucoma had a mean cost per patient screened of $922.77 (US) and a mean cost per detected case of $1098.67 (US).[8] However, there are no economic evaluations in literature which examine the cost-effectiveness of the use of telemedicine for glaucoma screening. Thus, the purpose of this cost-effectiveness analysis (CEA) was to examine the costs and benefits of teleglaucoma and to determine the cost-effectiveness of teleglaucoma as a screening device for glaucoma in comparison to the standard of care, which is in-person examination. This CEA took a third-party payer and Ministry of Health perspective. The targeted population included people living in rural Alberta who are at-risk of glaucoma. The long term benefits of teleglaucoma which included prevention of blindness from glaucoma was also

assessed. A portion of this chapter has been conditionally accepted for publication and is currently under second review.[11]

4.2 Methods

4.2.1 Study Design

A cost-effectiveness analysis was conducted using healthcare provider perspectives within rural Alberta, Canada.[11] Statistics Canada defines rural populations as areas with persons living outside centers with a population of 10,000 or fewer and outside areas with fewer than 400 persons per square kilometre.[12] Other than certain parts of Edmonton and Calgary, the majority of communities in Alberta are rural areas. It has been documented that 95% of Alberta is rural area.[13] The study population are patients at-risk of glaucoma, which includes those with diabetes and/or hypertension, family history of glaucoma, older adults, and concurrent ocular conditions in rural Alberta. Targeting at-risk populations has been suggested as a more efficient method of detecting glaucoma.[14] Teleglaucoma screening in the model was applied to a population aged 50 years and older at a frequency of one screening per year.[11] The model assumed teleglaucoma has the capacity for 300 people per year.[7,11] The time horizon was 30 years as glaucoma is a chronic, life-long condition.

4.2.2 Teleglaucoma Definition

There are several standardized characteristics of Teleglaucoma (Table 1). Teleglaucoma consists of standard ophthalmic instruments used for screening.

The main instruments are the fundus cameras, Heidelberg Retina Tomograph (HRT), and the optical coherence tomography (OCT), which produce digital imaging of the retina.[15-17] In addition, tonometers are used to measure the intraocular pressure. Gonioscopy, a test used to determine the angle between the iris and cornea, and perimetry, the visual field test, are also used for teleglaucoma screening. The retinal images and test results are sent via electronic systems. Thus, the essential part of teleglaucoma is the information systems which include the Secure Diagnostic Imaging (SDI) systems, ISDN installations, computers, and videoconferencing equipment. These equipment would be set up within a small clinic in the vicinity of the rural population.

Teleglaucoma requires at minimum technicians who are trained to screen the patients and to transfer the files to the ophthalmologist.[7,15] The teleglaucoma process is a quick process; the mean screening time is 8.8 minutes.[17] Once the images are sent to the ophthalmologist, the images and test results are then used for diagnosis. If the patient is diagnosed or determined as a glaucoma suspect, the patient is then referred to the ophthalmologist for a full consultation and receives the standard of care for glaucoma treatment.

4.2.3 Comparator Definition

The comparator for this study was in-person examination, the standard screening that occurs at the optometrists and/or ophthalmologists office. This type of screening is a more “passive” type of screening where patients have their routine eye examination; it is not necessarily a targeted screening for glaucoma.

However, patients with known risk-factors for glaucoma are screened specifically for glaucoma.

In-person examination uses the standard diagnostic instruments as described for teleglaucoma with the exception of the imaging transferring software.[5,15] The staff required are optometrists, technicians, and ophthalmologists.[8,15] For in-person examination, the patient visits the optometrist in person at the clinic for a full examination of the eye. If glaucoma is suspected the patient is then referred to an ophthalmologist. The ophthalmologists will perform several more diagnostic tests to diagnose glaucoma. Based on the diagnosis, the patient will receive treatment in accordance with the standard of care for glaucoma. If glaucoma is suspected the patient will continue to be monitored by the ophthalmologists.[6] For this study, in-person examination was considered “no-screening or passive screening” intervention. It is also the “do-nothing” approach as it is the standard of care for glaucoma screening.

4.2.4 Markov Model

Markov Modelling was used to model the four glaucoma health states (mild, moderate, severe, and blind).[11] TreeAge Pro 2009 was used to build the Markov Model (Appendix 4) consisting of the costs, benefits, and transitional probabilities of different health states. Incremental cost-effectiveness ratios (ICER) were developed in dollars per QALYs. Effectiveness was measured in QALYs and costs were used in Canadian dollars. The cycle for the Markov Model

represented one year and the ICERs following 30 cycles were established.[11] Assumptions that were used in the model is that:

- Individuals with glaucoma who were screened negative with teleglaucoma were assumed to be detected at the same probability of at-risk populations. They will have the same probabilities as being detected through in-person care.
- Individuals without glaucoma who were correctly screened negative can either remain at risk or transition to mild glaucoma at the transitional probability without treatment.
- Individuals with glaucoma who were seen by in-person care who were incorrectly detected as negative for glaucoma were assumed to have transitional probabilities based on untreated glaucoma.

In application, the implementation of teleglaucoma does not replace in-person care, but rather is additional to in-person care. Thus, the teleglaucoma arm of the decision tree, is displayed with combined costs and effect data of teleglaucoma and in-person care (Appendix 4). This model provides an overall outlook on total costs to run both programs at the same time in comparison to in-person examination.

4.2.5 Health States

There are four health states associated with glaucoma: mild, moderate, severe, and end-stage glaucoma, which is blindness.[6,18] Mild glaucoma is characterized by abnormalities of the optic nerve without any visual field

abnormalities. Moderate glaucoma is characterized by damage to the optic nerve and some peripheral vision loss. Severe glaucoma is the advanced stage of glaucoma characterized by severe optic nerve damage and advanced peripheral vision loss.[11] Blindness is characterized by a visual acuity of 20/200 or worst.[19] Blindness in this study refers only to blindness due to glaucoma as opposed to blindness due to other causes.

Glaucoma is a chronic condition with progressive ocular damage and vision loss. Patients will progress from one stage to the next and with successful treatments the patient will remain in the current health state. There is no cure for glaucoma and thus patients cannot transition to healthier states. Once a patient is blind, the patient will remain blind.

The Markov Model transitional states can be found in Figure 4.1. The progression of glaucoma through the health states are at higher probabilities when glaucoma is not detected early, not diagnosed, and/or left untreated (Table 4.2). The transitional probabilities are not time-dependent but rather depend on management of disease through treatments or no treatments.[9] If managed appropriately with proper medications and treatment the progression of glaucoma is delayed.[6] Patients who were detected positive with either teleglaucoma or in-person care were assumed to be treated. There was a 75% compliance with treatment and treatment efficacy was 50% as reported by literature.[9] Because the progression of glaucoma is dependent on individual characteristics and compliance to treatment, there is a degree of uncertainty with the transitional

probabilities. As a result, beta distributions will be applied to transitional probabilities and assessed through Probabilistic Sensitivity Analysis.

4.2.6 Costs

Technology Costs

There are three main components of teleglaucoma and each are associated with costs: human resources, information technology, and diagnostic equipment (Table 4.1).[15] The synthesis of teleglaucoma costs derived by Thomas et al. and the Ministry of Health Medical Procedures List were used as costing data sources.[17,21] Additional base costs of the teleglaucoma technology were reported by a study on effectiveness of tele-ophthalmology for glaucoma by Tuulonen.[7] All costs were converted to 2014 Canadian dollars and adjusted for inflation at 2.05%.[17,] Future costs were discounted at a 3% rate.[9,10]

Costs were divided by the number of patients serviced to determine the costs per patient and also to account for the differences in coverage between in-person care and teleglaucoma. Teleglaucoma was reported to service 300 people per year, while in-person care was reported to have 1379 glaucoma visits per year in rural Alberta.[7,22] Teleglaucoma requires training of graders on how to use the technology. The costs for training includes labour costs for two (full-time equivalents) trainers at the average Alberta salary ($50,000) and training resources.[23] Costs assumed a maximum two week training session and paid for trainees. The direct costs of teleglaucoma included the costs of equipment, set-up, overhead, utilities, and labour (Table 4.3).

Health State Costs

There are costs associated with living with glaucoma. Each health state requires different levels of medical treatments and drug therapies. In addition, each is associated with indirect costs such as health system costs, loss of productivity, additional vision aids, and modifications to home or work to compensate for vision loss. The costs associated with each health state was given by Lee et al study on resource consumption at different levels of severity of glaucoma.[23] All stages include the following direct costs: visits to ophthalmologists and/or optometrists, Humphrey Visual Field tests, medications, surgeries, and glaucoma testing (gonioscopies, nerve fiber thickness analysis and intraocular pressure diurnal).[24]

The stage at-risk was assumed to be equal to “Stage 0” of Lee’s criteria which constitutes a glaucoma suspect patient who is at-risk of glaucoma, but does not meet the criteria for clinical diagnosis.[24] The costs associated with the “at-risk” stage includes routine optometrists and/or ophthalmologist visits. The costs of blindness were reported by the Canadian National Institute for the Blind (CNIB).[25] The costs of blindness includes direct costs (vision aids and treatments) as well as indirect costs such as loss of productivity, caregiving assistance, etc. Table 4 summarizes the costs associated with each health state. The costs were derived to represent Alberta. In rural Alberta, there are limited nearby ophthalmic resources and travelling when blind becomes a costly endeavor.[13,22] Thus, uncertainty in costs of blindness was addressed using sensitivity analysis.

Patient Costs

Teleglaucoma has been reported to have direct reduction in costs to patients specifically in travel time, doctor wait times, assessment times, and transportation costs.[7,17,26] These costs were added to the costs associated with teleglaucoma and in-person care to be included in the analysis. The costs to patients for each intervention is summarized in Appendix 5. The following assumptions were applied to estimate costs:

- Travelling costs were assumed to be costs associated with personal automobiles and did not account for potential public transit costs. Distance travelled was converted into costs using current 2014 gas prices in Alberta ($1.26/L).[27]
- The Grossman Health Model regarding the consumption and investment demand for health was applied.[9,10] It is assumed there is a trade-off between time spent producing health and time spent producing other goods. Any investments in health are reduced by time lost to illness. Thus, there is a monetary value to time. This monetary value will be assumed as wage rate. Time spent waiting for doctor and travelling to and from clinics were converted to loss of productivity using Alberta average hourly wage $29.54.[23]

Total Costs

All costs were summed into initial and incremental costs and cost per patient screened was determined (Appendix 6). The initial costs were the fixed costs

such as the initial set up fees. The incremental costs included the patient costs, service costs, labour costs and costs associated with each health state. All costs were converted to present value Canadian dollars and future costs were discounted at a 3% rate. The willingness to pay applied was $40,000/QALY as reported by literature for ophthalmic interventions.[25] Uncertainties in estimated costs were addressed using probabilistic sensitivity analysis and applying gamma distributions (Appendix 7).

4.2.7 Effectiveness

The effectiveness of teleglaucoma is defined by its ability to detect glaucoma. This is measured as specificity and sensitivity of the equipment devices and the probability of being correctly screened as glaucoma positive, and correctly screened as glaucoma negative. The sensitivity of teleglaucoma is particularly important because it incorporates the false negatives. The false negatives are the patients who have the disease and are incorrectly detected as a negative test. This patient group will be told they do not have the disease and continue living as normal. However, with glaucoma, this is particularly crucial to avoid. Glaucoma is a silent thief of vision and if left untreated patient can lose substantial visual acuity as well as suffer from visual defects. Thus, the sensitivity of teleglaucoma is important to prevent glaucoma cases from leaving the clinic without appropriate medical care.

Several studies have tested the accuracy of teleglaucoma devices with gold standard diagnostic tools, but have reported results in kappa statistic

agreements.[28,29] However, not all studies used the same equipment and devices. In addition, most studies were performed outside of Canada, specifically in Kenya or India. From the literature and chapter 3, the specificity and sensitivity of teleglaucoma were reported as 86.5% and 78.6% respectively.[17]

The second aspect of effectiveness is the ability of screening devices to detect glaucoma at its early stages. The probabilities of each stage of glaucoma at time of screening were derived from a study examining the use of teleophthalmology.[30] Corresponding with the hypothesis, a greater proportion of individuals (46%) at mild glaucoma stage were detected with teleglaucoma.[30] The effectiveness of no screening (in-person care) was given by reported probability of glaucoma being detected in routine in-person care.[1] Fifty per cent of glaucoma patients are undetected and are unaware of their disease state.[1] The other 50%, when presented at in-person care, these glaucoma patients are usually at the advanced stages of the disease with progressive vision loss. The probabilities of each glaucoma health state detected at time of in-person care was derived from CNIB's Cost of Vision Loss Report.[1] Table 4.5 displays the probabilities of glaucoma detection with each intervention. It also displays those who were detected and at which health state they were in at time of screening.[1]

The effectiveness of teleglaucoma was also measured in its reduction of travel time and improved access to care for people living in rural Alberta and other remote, underserviced areas. Specifically, teleglaucoma has been associated with savings of 4906km in travel distance and 61.23 hours of travelling time.[17,26,31] The length of time spent at the doctor visit (includes wait

time and assessment time) with teleglaucoma was 78 minutes (~1.3 hours) whereas with in-person care it took 115 minutes (~1.91hours).[17,26]

4.2.8 Utilities

The effectiveness of teleglaucoma as stated above is mainly seen by its early detection, to initiate early treatment, to prevent progression of disease into advanced stages. Thus, its beneficial for preserving vision. Living in each glaucoma stage, specifically with vision loss, negatively affects one's HRQoL. With each glaucoma health state there is a progression of the disease. Thus with disease progression, there is a decline in HRQoL and decreased utility value. The utility value for each health state is 0.87, 0.79, 0.64, and 0.5, for mild, moderate, severe, and blindness, respectively.[32,33] These values are converted to QALYs, as the ultimate unit of effectiveness for the cost-effectiveness analysis. QALY incorporates both quality and quantity of life, specifically life expectancy, and quality of remaining life years. QALYs are the amount of years in a person's life that is adjusted to represent remaining life years in perfect quality.[9] It uses weights on time spent in different health states. Thus one year living in blind state (utility value =0.5) is equivalent to half a year living in perfect health (utility = 1.0) which means blind state is equivalent to 0.5 QALYs. Likewise the effect gained from living in mild, moderate, and severe glaucoma is thus 0.87 QALYs, 0.79 QALYs, and 0.64 QALYs, respectively.

4.2.9 Analysis Plan

This study analyzed the incremental costs, the incremental effect, and the ICER for teleglaucoma versus in-person examination. Deterministic and probabilistic sensitivity analyses were performed to assess the factors affecting cost-effectiveness. Markov Cohort Analysis by 30 stages was conducted to demonstrate the accumulated rewards, costs, and probabilities after 30 years. Monte Carlo Simulations with the application of second-order uncertainties and gamma and beta distributions were performed with 1000 samples. In addition, the analysis generated the distribution of the ICERs by probability, the cost-effectiveness scatterplots, and the impact of willingness-to-pay on the probability of ICERs within an acceptability curve.

Sensitivity Analysis

Certain parameters within the model have uncertainties as discussed above. Sensitivity analysis was conducted to determine if the uncertainties affect the stability of the results. Deterministic sensitivity analysis was used to determine any effects of uncertainty of costs of blindness, transitional probabilities (at-risk to mild glaucoma and severe to blind states), and probability of glaucoma within the population. The estimated probability of glaucoma contains uncertainty as most cases of glaucoma go undetected and also there is potential uncertainty in the generalizability of prevalence rates to rural Alberta. These parameters were varied by 20% within the analysis (Table 4.2, Table 4.4). Tornado diagrams were used to give parameters that have the most effect on

cost-effectiveness. Probabilistic Sensitivity Analysis was also conducted to assess uncertainty using gamma and beta distributions for uncertain costs and probabilities respectively (Appendix 7).

4.3 Results

4.3.1 Incremental Cost-Effectiveness Ratio

The ICER for teleglaucoma screening versus in-person examination (no-screening) was established in *TreeAge 2009* displaying the ratio of incremental costs (Canadian dollars) and incremental effectiveness (QALYs) at a discounted rate of 3% (Table 4.6).[11]

Teleglaucoma demonstrated to be more cost-effective than in-person care for detecting glaucoma; the ICER was $47.60/QALY.[11] This means that spending an additional $47.60 for each patient screened with teleglaucoma will give an additional QALY in comparison to in-person screening. The results also indicated that teleglaucoma costs less than in-person screening when adjusted for per patient costs and also it was more effective. Thus, the no screening option (in-person examination) is dominated by teleglaucoma screening (Figure 4.2). In most cases, cost-effectiveness analysis are not performed under these conditions (more effective, less costly). However, this study included long-term effectiveness, which was not investigated previously in literature and thus this analysis has established new information.

4.3.2 Markov Cohort Analysis

Based on Markov Model principles, transitional probabilities are independent of previous health states and they determine the proportion of individuals who transition to other heath states per cycle.[9,10] Markov Cohort Analysis was conducted with 30 cycles representing 30 years.

After 30 years, teleglaucoma showed rewards for people with glaucoma who were initially screened positive. The total reward for teleglaucoma was 15.7 QALYs, which was 1.1 less than rewards from in-person care (Table 4.7).[11] However, the cumulative costs per patient for in-person care was almost 3.5 times that of teleglaucoma after 30 years, which indicated the cost-saving associated with teleglaucoma screening. For both interventions, after 30 years the majority of patients were blind, however it was 24% less in teleglaucoma screening.[11] Teleglaucoma also had a greater probability of preventing glaucoma patients from progressing as 15% remained in the mild stage of glaucoma compared to 2% with no screening.

The Markov Probability Analysis displayed how the probability of each health state changes over the study time horizon in patients who were detected positive for glaucoma with either intervention (Figure 4.2).[11] The results demonstrated that the probability of being at-risk for glaucoma and moderate glaucoma over 30 years (30 stages) remains relatively the same in teleglaucoma versus in-person care. The probability of being in mild glaucoma is higher with teleglaucoma screening, but in both interventions this probability declines with time. Similar to

previous results, the probability of being blind was greater with in-person care than with teleglaucoma (the concave down increasing trend of the blind state curve in Figure 4.2b displays a closely exponential trend).[11] This indicated that teleglaucoma is more effective at preventing the probability of blindness in glaucoma patients.

4.3.3 Deterministic Sensitivity Analysis

Deterministic sensitivity analysis was used to determine the effects of uncertainty on the ICER results. One-way sensitivity analyses were performed on the following variables: the costs of blindness, the transitional probabilities for at-risk to mild glaucoma and severe glaucoma to blind states (with and without treatment). The results demonstrated that changing (+/- 20%) the costs of blindness caused changes in the ICERs for both strategies. Teleglaucoma had higher ICERs than inpatient screening (Figure 4.3).[11] The cost-effectiveness of teleglaucoma is affected by the costs of blindness: as costs of blindness increases the ICER for teleglaucoma becomes smaller.

As shown in Figure 4.3d, the ICERs of inpatient screening remained unchanged while the ICER of teleglaucoma increased very slightly as the transitional probability of blindness increased.[11] With better treatment of glaucoma, which prevents patients from becoming blind, teleglaucoma becomes more cost-effective (Figure 4.3d).[11]

The tornado diagram gives the parameters with the most effect on cost-effectiveness at a willingness to pay of $40,000/QALY (Figure 4.4).[11] It displays

that the uncertainty within the prevalence of glaucoma has the most effect on the ICER and it has the largest range of net monetary benefits. The results suggest the transitional probabilities for at-risk to mild and severe to blind have more of an effect on the cost-effectiveness of teleglaucoma as well as the cost of blindness. Whereas, the transitional probability for severe to blind without treatment and at-risk to mild with treatment had less effect on the cost-effectiveness of teleglaucoma.

4.3.4 Probabilistic Sensitivity Analysis

Gamma and beta distributions were applied to the Markov Model. Monte Carlo Simulation second order was conducted and the statistics report gave a mean cost of teleglaucoma as $866.90 ± 113.10 per patient screened compared to in-person screening which has a mean of $4419.8 ± 1044.70. The results showed teleglaucoma costs less per patient than in-person screening.

The results of the Cost-effectiveness scatterplot demonstrate that there is a greater uncertainty with the costs and effectiveness of “in-person screening” (in-person care) as the dots of the graph are widely spread apart giving costs from approximately $3K-8K (Figure 4.4).[11] However, there is less uncertainty with the costs of teleglaucoma, since the dots are tightly plotted around $1K (Figure 4.4).[11] This means that the ICER of in-person care is more sensitive to the costs than the ICER of teleglaucoma whereas teleglaucoma ICER is more sensitive to the effectiveness in comparison to in-person care. The results of the sensitivity analysis on willingness to pay demonstrate that neither teleglaucoma nor in-

person care is sensitive to changes in WTP as the line remains relatively constant as WTP changes (Figure 4.5).[11] Only after WTP increases above $60,000, the probability of cost-effectiveness for teleglaucoma becomes slightly less cost-effective versus in-person screening which becomes slightly more cost-effective. However, in comparison to in-person screening teleglaucoma is 100% more cost-effective.

4.4 Discussion

Teleglaucoma is beneficial to remote areas as the physician is not required to see patients in person. This reduces wait times and shortens the length of ophthalmic consultations. Teleglaucoma avoids long distance travel and time wasted on commuting. Our results demonstrated the direct benefits to patients was a cost savings of ~$2474.60 with teleglaucoma. The early detection approach of teleglaucoma successfully reduced the probability of patients at the blind stage of glaucoma by 24% and maintained 13% more patients at the mild stage glaucoma in comparison to in-person care. The long-term benefits of early detection was confirmed by this CEA with greater cumulative rewards and cost savings 30 years post-detection. When assessed on its own, teleglaucoma was more cost-effective than in-person care with an ICER of -$27,460 per QALY (cost per patient serviced) meaning teleglaucoma saved $27,460 per QALY gained relative to in-person examination. The large direct patient savings and reduced costs of blindness due to preservation of vision, mainly accounted for its effectiveness. The ICER of teleglaucoma was only sensitive to the probability of

glaucoma. This is logical since positive predictive values of screening tools fluctuate with changing prevalence rates and changing prevalence rates will alter the probability of glaucoma. As the probability of having glaucoma increases, teleglaucoma had greater cost-effectiveness.

At a willingness to pay of $40,000/QALY, teleglaucoma is cost-effective when compared with in-person care.[25] In addition, the World Health Organization provides the threshold for cost-effective interventions: an intervention is considered cost-effective if the ICER associated with implementation of the intervention is less than the country's GDP.[34] Teleglaucoma has an ICER below Alberta's GDP and thus, teleglaucoma is cost-effective for Alberta's population.

Several studies have analyzed the effectiveness of teleglaucoma in terms of its ability to detect glaucoma and proposed reduction in direct patient costs, however, none have produced a complete cost-effectiveness analysis.[17] Analysis of teleophthalmology for other ocular conditions such as diabetic retinopathy, have also shown to be cost-effective with ICERs of $1320/QALY in a similar rural setting based on the data of 326 patients from rural India.[35]

The strength of this study is it indicated that although the base cost of teleglaucoma is large, the variable cost is lower per year. In return, the benefits outweigh costs over time. In addition, this study includes indirect costs such as loss of productivity and opportunity costs of time. By including the patient, the healthcare provider, as well as the Ministry of Alberta perspectives, a societal perspective is developed providing a broad scope on the cost-effectiveness of

teleglaucoma. This CEA is focused on screening for a targeted population who is above the age of 50 years and at-risk of glaucoma in rural Alberta, which is another strength of this study. Mass screening of total populations are not cost-effective as it wastes resources with small benefits. In addition, this CEA applied Markov Modelling to illustrate the progression of glaucoma through transitional health states over time. This is beneficial to predict the long-term benefits of teleglaucoma. Costs were also discounted at a 3.0% rate to account for future value. Most studies have reported only the patient's present benefits at time of the teleglaucoma screening, but have not analyzed the aftermath. Thus, with a time horizon of 30 years this CEA contributes to literature by illustrating teleglaucoma enables early detection, and, as a result, it delays the progression of glaucoma and preserves vision.

One of the limitations for the CEA is that because no studies have analyzed the long-term benefits of teleglaucoma, estimates of transitional probabilities were derived from non-teleglaucoma studies. In addition, there is a lack of RCT data on teleglaucoma as most studies are observational. Of the observational studies that did look at the effectiveness of teleglaucoma, most focused on diagnostic accuracy, patient satisfaction, and reduced patient costs, but did not examine clinically relevant outcomes such as reduction in patients with vision loss.

In conclusion, a cost-effectiveness analysis of teleglaucoma was successfully performed to demonstrate that implementing teleglaucoma in rural Alberta and targeting at-risk population is cost-effective in comparison to no

screening. Early detection of glaucoma allows necessary medical care to prevent progression of the disease. Glaucoma is a chronic progressive disease with no cure and thus this CEA provides valuable prognosis information. Teleglaucoma can have long-term benefits on preservation of vision in those with glaucoma.

4.5 Literature Cited

1. Canadian National Institute for the Blind (CNIB) and the Canadian Ophthalmology Society (2009) Costs of vision loss in Canada. Access Economics Pty Limited Available: http://www.cnib.ca/eng/cnib%20document%20library/research/covl_full_report.pdf.

2. Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ et al. (2006) The economic burden of major adult disorders in the United States. Arch Ophthalmol Dec; 124(12): 1754-60.

3. Hatt S, Wormald R, Burr J (2006) Screening for prevention of optic nerve damage due to chronic open angle glaucoma. Cochrane Database of Systematic Reviews Issue 4. Art. No.: CD006129. DOI:0.1002/14651858.CD006129.pub2.

4. Burr JM, Mowatt G, Hernández R, et al. (2007) The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess. 11(41):1–190.

5. Allingham, R. R., Damji K, Shields, M. B. et al. (2011). Shields' textbook of glaucoma. 6th ed. Philadelphia: Lippincott Williams & Wilkins.

6. Gupta, D. (2005). Glaucoma diagnosis and management. Philadelphia: Lippincott Williams & Wilkins

7. Tuulonen A, Ohinmaa A, Alanko H, et al. (1999) The application of teleophthalmology in examining patients with glaucoma: a pilot study. J Glaucoma 8: 367–73.

8. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening:

A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

9. Drummond MF, Sculpher MJ, Torrance GW, et al. (2005) Methods for the Economic Evaluation of Health Care Programmes, 3rd edition. Oxford University Press.

10. Gray AM, Clarke PM, Wolstenholme J, et al. (2010) Applied Methods of Cost-effectiveness Analysis in Health Care. Oxford University Press.

11. Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

12. Statistics Canada (2011) 2011 Census Population. Available: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo62j-eng.htm Accessed 2015 Feb 20.

13. Arcand A, Lefebvre M (2012) Alberta's rural communities their economic contribution to Alberta and Canada. The Conference Board of Canada. Available: http://www1.agric.gov.ab.ca/$Department/deptdocs.nsf/all/csi14195/$FILE/alberta-rural-communities-report.pdf Accessed 2015 Mar 21

14. Mayor, S. (2007) Targeted screening may be a cost effective way to detect glaucoma. BMJ : British Medical Journal, 335(7630), 1114. doi:10.1136/bmj.39412.508993.94

15. Kassam F, Amin S, Sogbesan E, et al. (2012) The use of teleglaucoma at the University of Alberta. J Telemed Telecare 8: 367.

16. Amin S, Damji K, Kassam F, et al. (2012) In-house patient-centered teleglaucoma improves access and efficiency for glaucoma suspects and those with early stages of open-angle glaucoma (OAG). Canadian Ophthalmology Society Annual Meeting.

17. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

18. Fellman R, Mattox C, Ross K, et al. (2011) Savvy Coder: Coding & Reimbursement. Know the New Glaucoma Staging Codes. American

Academy of Ophthalmology, EyeNet 65-66. Available: http://www.aao.org/publications/eyenet/201110/coder.cfm?RenderForPrint=1& Accessed 2015 Mar 29.

19. American Foundation for the Blind (2008) Key Definitions of Statistics Terms. Available: http://www.afb.org/info/blindness-statistics/key-definitions-of-statistical-terms/25 Accessed 2015 Mar 29.

20. Boivin. (1996). Cost effectiveness of screening for primary open angle glaucoma. Journal of Medical Screening 1996;3:154-163.

21. Government of Alberta (2014). Medical Procedures Lists. Available online: <http://www.health.alberta.ca/documents/SOMB-Medical-Procedures-2014-04.pdf>

22. Rudinsky C, Tennant M, Johnson J, et al. (2009). Alberta Atlas 2009: Chapter 8 – Diabetes and Eye Disease in Alberta. Alberta Disease Surveillance System. Available: http://www.albertadiabetes.ca/pdf/atlas/09/Atlas-8%28web%29.pdf. Accessed 2014 Mar 29.

23. Statistics Canada (StatsCan) (2014). Earnings, average weekly, by province and territory. Available online <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr79-eng.htm>

24. Lee, et al. (2006). A Multicenter, Retrospective Pilot Study of Resource Use and Costs Associated with Severity of Disease in Glaucoma. Archives of Ophthalmology, 12-19.

25. CNIB and the Canadian Ophthalmology Society (2008) Costs of vision loss in Canada: Summary report. Available online: http://www.cnib.ca/eng/CNIB%20Document%20Library/Research/Summaryreport_Covl.pdf

26. Arora S, Rudnisky C, Damji K (2014) Improved Access and Cycle Time with an “In-house” patient-centered teleglaucoma program versus traditional in-person assessment. Telemed J E-Health 20(5):439–45. doi: 10.1089/tmj.2013.0241

27. Canadian Broadcasting Corporation (CBC). (2014). Alberta Gas Prices. http://www.cbc.ca/calgary/features/gasprices/

28. Kiage D, Kherani I, Gichuhi S, et al. (2013) The Muranga Teleophthalmology Study: Comparison of Virtual (Teleglaucoma) with in-person clinical assessment to diagnose glaucoma. Middle East Afr J Ophthalmol 20(2): 150–157.

29. Gupta S, Sinha SK, Dagar AB (2013) Evaluation of the effectiveness of diagnostic & management decision by teleophthalmology using indigenous equipment in comparison with in-clinic assessment of patients. Indian J Med Res 138: 531–5.

30. Pasquale Asefzadeh B, Dunphy RW et al. (2007) Detection of glaucoma-like optic discs in a diabetes teleretinal program. Optometry; 78:657-663.

31. Sogbesan E, Rudnisky C, Tennant M, Damji K (2010) Time and cost-benefit analysis of a collaborative web-based stereoscopic teleglaucoma care model. Canadian Ophthalmology Society Annual Meeting.

32. Burr JM, Kilonzo M, Vale L, et al. (2007) Developing a preference-based glaucoma utility index using a discrete choice experiment. Optom Vis Sci 84, 797–808.

33. Tengs TO, Wallace A (2000) One thousand health-related quality-of-life estimates. Med Care 38, 583–637.

34. Tan-Torres Edejer T, Baltussen R, Adam T (Eds.) et al. (2003) Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis, World Health Organization, Geneva. Available: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf

35. Rachepelle S, Legood R, Alavi Y, et al. (2013). The Cost utility of telemedicine to screen for diabetic retinopathy in India. American Academy of Ophthalmology.

36. Stein, J D, Kim D, Peck W, et al. (2012). Cost-Effectiveness of Medications Compared With Laser Trabeculoplasty in Patients With Newly Diagnosed Open-Angle Glaucoma. Arch.Ophthalmol. doi:10.1001/archophthalmol.2011.2727

37. Fletchner R (2004). Can we model risk in ocular hypertension? Review of Ophthalmology. Available online: <http://www.revophth.com/content/d/glaucoma_management/i/1324/c/25433/>

38. Chen (2014). How Frequently Does Blindness Develop Among Patients With Primary Open-Angle Glaucoma? With Ocular Hypertension? Healio Consultation. http://www.healio.com/ophthalmology/curbside-consultation/%7B568973d0-899e-4622-bf17-bf3d730de14f%7D/how-frequently-does-blin

4.6 Tables

Table 4.1: Standardized Teleglaucoma Equipment

Human Resources	Information Technology	Screening Equipment	Examinations
Ophthalmic technicians, Physicians' glaucoma specialists/ ophthalmologists, Graders, Optometrist	Secure Diagnostic Imaging (SDI) system, Videoconferencing equipment, Computer systems and software	Retinal camera, Tonometer, Devices to measure central corneal thickness, Frequency Doubling Technology (FDT) or Humphrey Visual Field test, Optical Coherence Tomography, Slit lamp, Gonioscope, Retinal camera, Devices to measure central corneal thickness	Medical & family history, Visual acuity, IOP, CCT, OCT, Slit lamp, Gonioscopy, Visual field, Pupil equal and reactive to light (PERL) or relative afferent pupillary defect (RAPD), Fundus photographs, Ancillary tests

Footnote: Thomas S-M, Jeyaraman MM, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

Table 4.2: Transitional Probabilities for Glaucoma Health States

	Health States	Transitional Probability	Sensitivity Analysis Range	Reference
Treated	At-Risk to Mild Glaucoma	0.20	0.16-0.24	Stein, 2012[35]
	Mild to Moderate Glaucoma	0.04		
	Moderate to Severe Glaucoma	0.10		
	Severe Glaucoma to Blind	0.15	0.12-0.18	
Untreated	At-Risk to Mild Glaucoma	0.48	0.38-0.58	Fechtner, 2004[36]
	Mild to Moderate Glaucoma	0.26		Chen, 2014[37]
	Moderate to Severe Glaucoma	0.5		
	Severe Glaucoma to Blind	0.5	0.4-0.6	Fechtner, 2004[36]

Table 4.3: Direct Costs of Teleglaucoma and in-person Care

	Teleglaucoma	**in-person Care**
	Total Fixed Costs ($)	
Set-up (Service and Training)	416,600	243,146
Technology Equipment	1,256,142	329,833
	Variable Costs ($ costs per patient screened)	
Labour	348	248.98
Service	370.89	309.90

Derivation of costs are found in Appendix 8.

Table 4.4: Costs associated with each health state

Health State	Costs ($)	Sensitivity Analysis
At-Risk	623	
Mild Glaucoma	1480	
Moderate Glaucoma	3682	
Severe Glaucoma	4975	
Blindness	33666	26,932.80 - 40399.20

Derivations of costs can be found in Appendix 9.

Table 4.5: Probabilities of glaucoma detection and associated health states

	Probability of Being Detection		Probability of each health state detected				
	Sensitivity	Specificity	At-risk	Mild	Moderate	Severe	Blind
Teleglaucoma	0.59	0.96	0.03	0.46	0.5099	0.0001	0
in-person care	0.50	0.50	0	0.08	0.52	0.30	0.1

Table 4.6: Summary of ICER Data

Strategy	Cost	Incremental Cost	Effect	Incremental Effect	Cost/Effect	ICER
Teleglaucoma Screening	871.54		18.32		47.57	
in-person Screening	4441.42	3569.88	18.19	-0.12	244.05	(Dominated)

Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Table 4.7: Accumulate Rewards, Costs, and Probabilities after 30 years

	Cumulative Costs ($)	Cumulative Rewards (QALY)	Probability at each health state				
			At-Risk	Mild	Moderate	Severe	Blind
Teleglaucoma	1155.45	15.7	3.71E-05	0.15	0.10	0.09	0.65
In-person/ no screening	4035.19	16.8	0	0.02	0.04	0.05	0.89

Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

4.7 Figures

Figure 4.1: Markov Model Transitional Health States

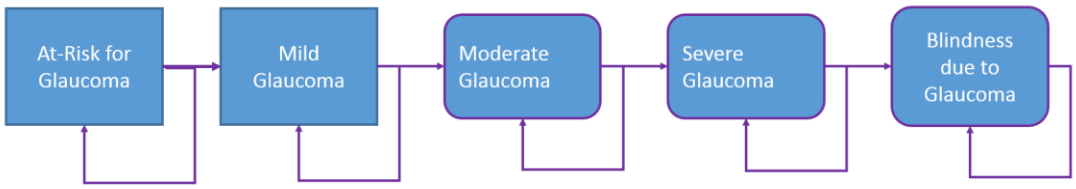
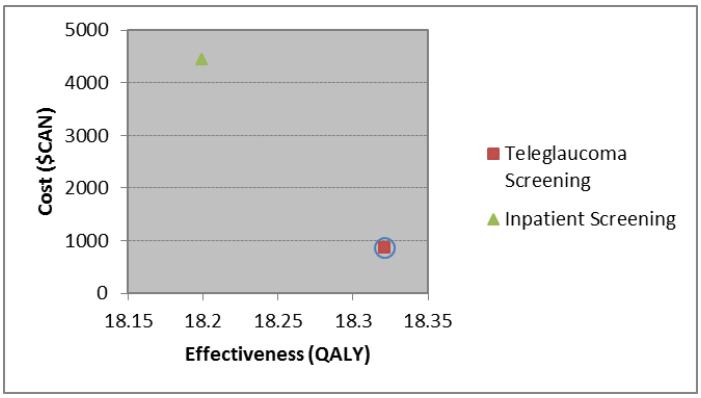
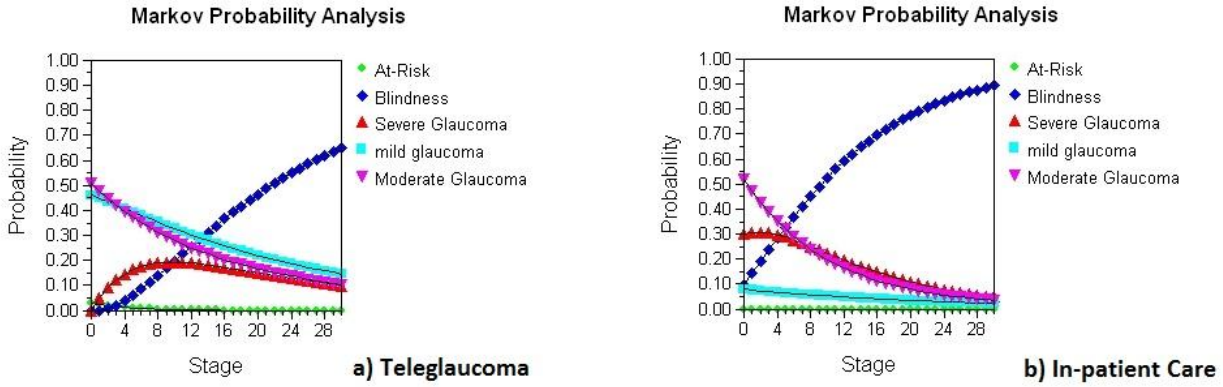


Figure 4.2: Cost-Effectiveness Analysis



Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Figure 4.3: Markov Probability Analysis of Health States



Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Figure 4.4: DSA One-Way Sensitivity Analysis

Figure 4.4a. Variable: Cost of blindness

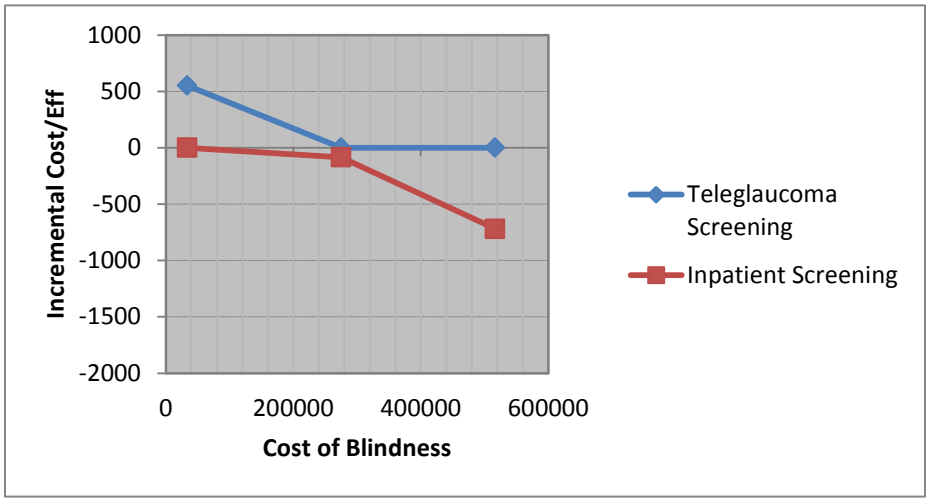


Figure 4.4b. Variable: Probability of Transitioning to Mild Stage Glaucoma

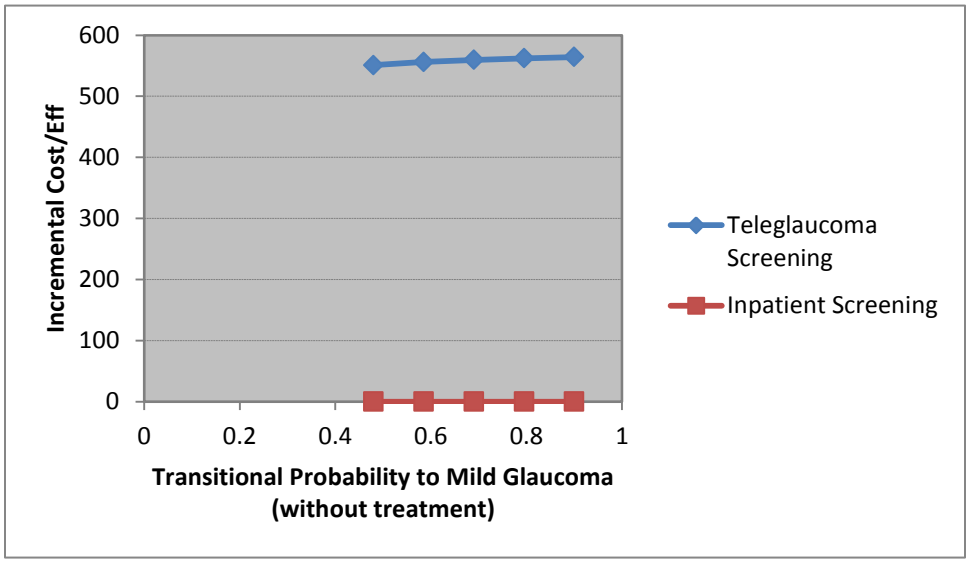


Figure 4.4c. Variable: Transitional Probability to Blind stage Glaucoma

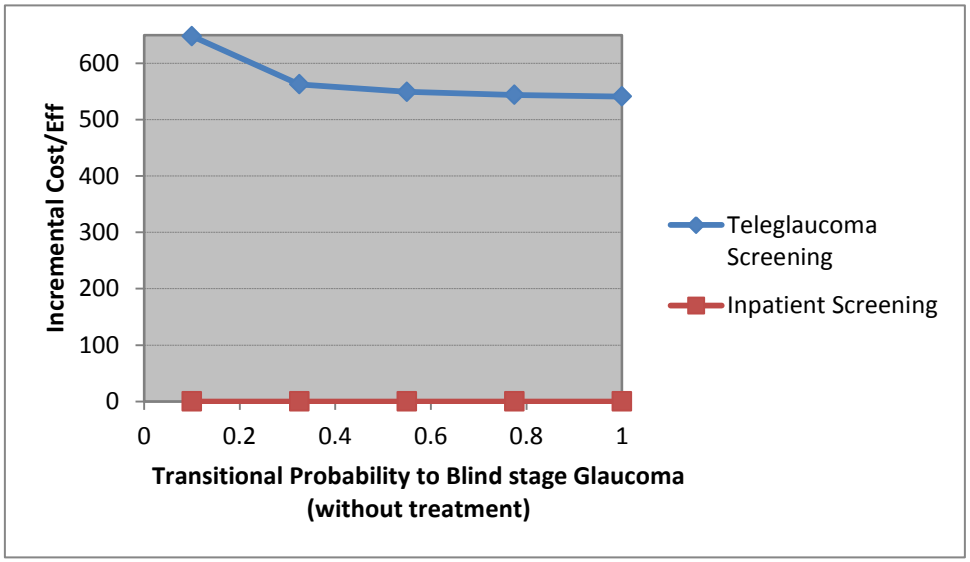
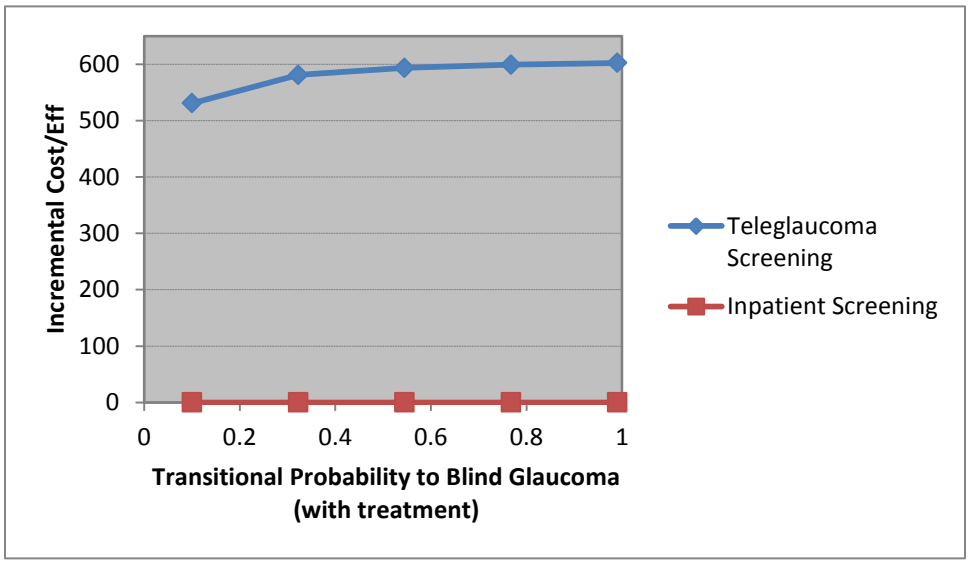
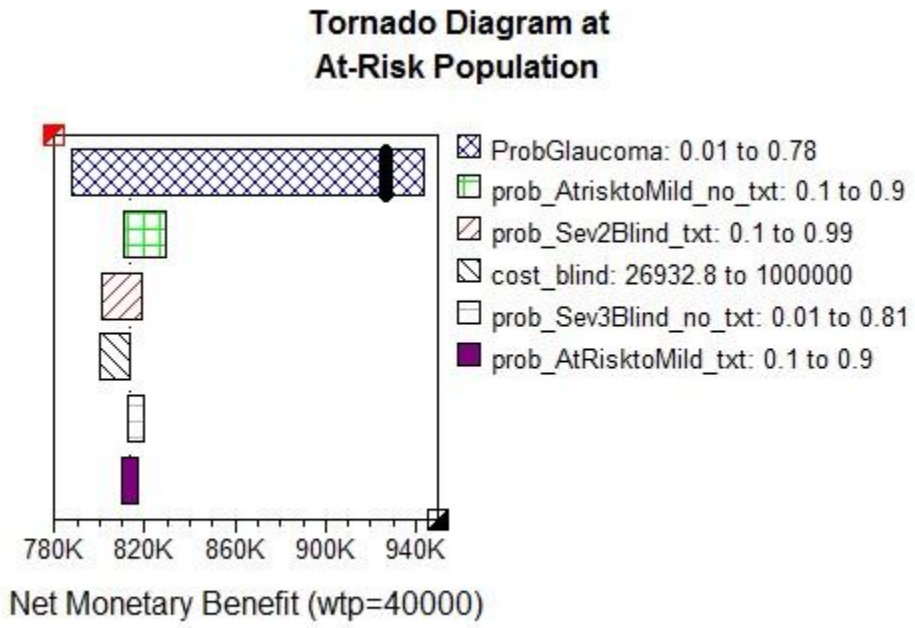


Figure 4.4d. Variable: Transitional Probability to Blind Glaucoma



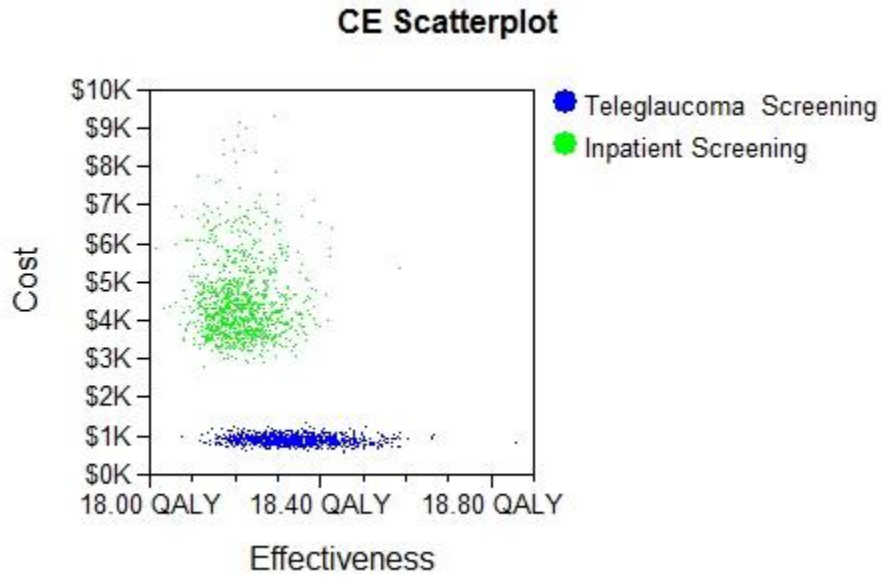
Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Figure 4.5: Tornado Diagram for At-Risk Population



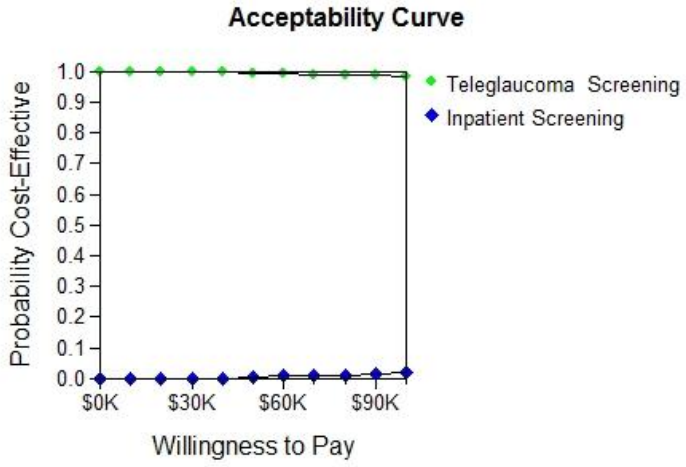
Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Figure 4.6: Cost-Effectiveness Scatterplot



Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Figure 4.7: Acceptability Curve



Footnote: Thomas S, Hodge WG, Malvankar-Mehta MS (2015). The Cost-Effectiveness Analysis of Teleglaucoma Screening Device. PLoS ONE (under second review 2015 June 7).

Chapter 5 Integrated Discussion

5.1 Overview

This chapter outlines the thesis results, interpretations, and generates the thesis conclusions. In summary, the objectives of the thesis were (1) to determine the effectiveness of teleglaucoma in its capability to accurately discriminate between positive and negative cases and (2) to determine the cost-effectiveness of teleglaucoma as a screening device.

5.2 Integrated Discussion of Thesis Results

This thesis synthesized published and unpublished research literature on the diagnostic accuracy of teleglaucoma. The meta-analysis found that the specificity and sensitivity were 0.79 [0.67, 0.88] and 0.83 [0.77, 0.88] respectively. The Canadian Ophthalmology Society (COS) criteria for the minimum effectiveness of tele-ophthalmology is a sensitivity of at least 80% and a specificity of at least 90%.[1] Thus, according to COS standards teleglaucoma does not meet the minimum requirements for an effective screening tool. However, it is important to note that in comparison to the standard of care, teleglaucoma had a greater specificity than in-person examination, but was not as sensitive as in-person examination. Thus, although teleglaucoma does not meet Canadian standards, it is more effective than the current practice.

Teleglaucoma demonstrated low false negative and high true positive rates. This is an indication of a good screening tool for glaucoma.[2] Glaucoma is a progressive disease that becomes worst when untreated. False positive cases

are left untreated and may progress to advanced stages of the disease.[2] For glaucoma specifically, it is important to detect the disease earlier to allow for early intervention and to prevent vision loss. Thus, this thesis has successfully demonstrated that teleglaucoma is beneficial to preventing visual impairment overall. However, the false positive rates are higher than in-person examination which seemingly introduces potential issues related to teleglaucoma.

A false positive means a patient thinks they have the disease, when they actually do not. With some diseases such as cancer, the patient may experience depression and psychological stress as a response to their screening result. However, with glaucoma, because the disease progression is slowed with treatment, the likelihood of serious consequences is low. This in return removes the risk of serious patient psychological consequences. In addition, the confirmatory test for glaucoma occurs within two months which is a relatively short time for a patient to wait to confirm their disease status. Prior to screening the patient receives consultation on the consequences of test results to ensure the patient is informed and to minimize the physiological risks of false positives. The confirmatory diagnosis conducted by the ophthalmologist involves very minimal risks.[2] Thus although, generally speaking a false positive is not good practice, with glaucoma there is very minimal risk to patient.

In addition, the results were based on optimizing the use of several glaucoma diagnostic instruments for screening. Several studies have reported the differences in diagnostic accuracy based on the various combinations of diagnostic instruments. With greater amounts of diagnostic instruments used to

examine glaucoma patients, the higher the accuracy of the screening process. The instruments used in this analysis, which defined teleglaucoma, were based on the minimum requirements set by Canadian Medical standards.[3]

In addition, teleglaucoma was able to detect greater proportions of glaucoma cases in comparison to in-person examination. This was an important finding as early detection plays an important role in preventing glaucoma progression. If caught early and treatment is initiated, glaucoma can be managed and patients can have preserved vision. The long term benefits of teleglaucoma found that in comparison to in-person examination, teleglaucoma prevents more cases of blindness.

Blindness lowers one's health-related quality of life (HRQoL) and limits one's independence. As glaucoma progresses through its health states, the quality of adjusted life years (QALYs) declines. The "blindness" health state is represented by 0.5 QALYs whereas the "at-risk" health state is represented by 0.87 QALYs.[4,5] As glaucoma progresses to advance stages it also becomes more costly to manage and treat. Moreover, it is expected that if teleglaucoma detects more cases of glaucoma and at earlier stages, then blindness can be prevented. This study successfully found that teleglaucoma prevents 24% of cases, in the long term, in comparison to in-person examination.

The second section of this thesis examined the cost implications of teleglaucoma. The direct and indirect costs of teleglaucoma system, which were synthesized systematically through the meta-analysis, were applied to the

Markov Model. The costs and the measure of quality of life of each health states were included in the analysis. Through the meta-analysis, the effectiveness of teleglaucoma was measured in specificity and sensitivity and was applied to the Markov Model. When taking all costs into consideration, teleglaucoma displayed reduction of costs. Furthermore, in terms of the effectiveness of teleglaucoma, this thesis found that teleglaucoma added 0.12 QALYs per each patient screened. This is a significant improvement in HRQoL when taking into consideration the time frame. The analysis used an annual time frame and all costs and benefits are thus based on yearly outcomes. Therefore, although a 0.12 QALY increase may not be a large impact over many years, a 0.12 QALY increase per year is a substantial difference in HRQoL. In conclusion, it was found that teleglaucoma is more cost-effective than in-person examination.

5.3 Thesis Limitations and Knowledge Gaps in Current Literature

There were limitations within this thesis study. The systematic review included studies written in English only. By excluding potential articles based on language, this may bias the results. It would essentially produce results valid to English speaking countries mainly. Statistically, this reduces sample size, whereby limiting the power of the results.

The quality of the study evidence varied and despite variation, all studies were included in the systematic review and meta-analysis. The quality of evidence was based on the risk of bias, imprecision, inconsistency, and

indirectness.[6-11] Of the 45 studies included in the systematic review, only 17 were of high quality based on the GRADE guidelines. High quality studies are those that have a high confidence that the true effect lies close to that of the estimate effect based on the fact there is no or minimal bias.[6-11] Thus, the majority of studies provided quality of evidence which were of low or moderate levels. The quality of evidence limits the validity of the results and thus, in return limits the accuracy of the synthesized results.

The meta-analysis section took into account the sample size and standard errors of each study which minimizes the risk of bias. However, all studies were observational studies and this reduces the quality of evidence. Observational studies lack a controlled environment and patients are not necessarily randomized.[12] This reduces the confidence that the treatment intervention is responsible for the differences in results. In contrast, randomized control trials (RCT) provide high level quality of evidence and due to gaps in the research literature; no RCTs have been conducted on teleglaucoma.[12,13] Observational studies provide a moderately good level of evidence, however they cannot control for all factors that may influence the study results. This indicates the need for more RCTs on this topic. Nonetheless, as the effectiveness of teleglaucoma includes the healthcare service quality, it is beneficial to highlight the teleglaucoma service in real-time through observational studies.

In addition, there was variability in the clinical characteristics reported by studies. Some studies focused on the specificity and sensitivity of teleglaucoma only and did not include a comparator. Some studies used various technologies

as part of their teleglaucoma system. There is expected variation in the technology quality and to minimize bias, only current studies were included.

Another limitation of the systematic review is the sample size. There were only ten studies used in the meta-analysis section. Of those ten studies, only five compared teleglaucoma to a comparator. When conducting a systematic review, the larger the sample size, the more evidence it will provide. Sample size is important for statistical reasons. For instance, the smaller the sample size, the more standard error and the lower the power of the results.[14] It also limits the confidence in the results. Thus, a sample size of ten is fairly small. Unfortunately, systematic reviews are dependent on the literature. Although, a comprehensive systematic search of published and unpublished literature was conducted, the results may not be representative of the actual service quality due to research gaps in literature. This suggests more literature is required on the effectiveness of teleglaucoma in general, and also on teleglaucoma in comparison to in-person examination.

Common bias affecting systematic reviews is publication bias which is the selective publication of certain types of studies.[12] To minimize publication bias, published and unpublished research databases were searched and articles from both sources were included. Thus, from the assessment, publication bias was minimal in this systematic review.

There were a few assumptions made during the CEA that may limit the external validity of this thesis. The main limitation is the study population; this

analysis applies only to rural populations, more specifically rural Alberta. Therefore, all costs, the healthcare system model, glaucoma prevalence, and patient demographics derived were based on Alberta. Importantly, the distance required for patients to travel is based on distances in Alberta. The cost-effectiveness of teleglaucoma is highly dependent on patient savings from the reduction in travel distance, time, and costs. Thus, the external validity of the study is restricted to populations similar to Alberta. In order to determine if teleglaucoma is cost-effective for a specific area, a CEA based on that specific population is required, as distances, currencies, and patient demographics change according to area. Importantly, the prevalence of glaucoma in the study population effects the cost-effectiveness. If the prevalence of glaucoma is higher, teleglaucoma becomes more cost-effective. This thesis assumed a prevalence of glaucoma found in Alberta, which may or may not be similar to other provinces or populations.

There was limited access to official costing sources such as specific Alberta hospital budgets. Thus, the actual costs for servicing a teleglaucoma clinic in its totality could not be determined accurately. Labour costs were estimated based on average Alberta physician and healthcare provider incomes. The costs used in the analysis were derived from published data and expert opinion. Thus, the total fixed and variable costs are estimates based on quotes from research literature required to service a teleglaucoma system. Some of the research literature were Canadian, but the majority of costing sources were European or American studies which may not represent Alberta best. Because of

the lack of official data sources, this thesis made assumptions that the costs would be similar in Alberta. Where possible, hospital data from London, Ontario from 2014 was used to at least have current and Canadian data. Examples of these estimates were the costs of ophthalmic instruments. Likewise, the costs of the comparator intervention were also derived from estimates, quotes, and published data which may not accurately represent Alberta. These limitations and resulting assumptions can create some inaccuracies in the results of the CEA and the internal validity of the costing analysis. It can bias the results in either way: cause teleglaucoma to become more cost-effective or in-person examination to become more cost-effective.

From the thesis results, a large proportion of teleglaucoma cost-savings was attributed to the reduction in direct patient costs (travel and wait times). Although travel times and wait time were sourced from published research literature based on Alberta's population, there were some limitations in the translation of data into costs. Firstly, only a few studies reported the travel distances and wait times, thus the power was limited by sample size. Secondly, the conversion of wait times and travel times into productivity loss was based on the assumption that patients were employed and earned an average Alberta salary. Glaucoma is a disease of the elderly and a proportion of patients may not be employed, but rather retired. The employment status and exact salaries of glaucoma patients at the Alberta teleglaucoma clinics are inaccessible and thus estimates had to be used.

Nevertheless, this raises an important issue of value of patient's time. Although, the patient is unemployed and may not have employment income, firstly, they may have income from other sources (such as pensions, RRSPs, or investment incomes). These sources of income are private data and may not be reported in literature.[15] As a result, income from other sources are challenging to quantify and estimate. Secondly, based on the Grossman model, it can be argued that those who are unemployed should not have the same monetary value as employed people and rather have a lower monetary value.[16] This is ethically incorrect because a person's time is valuable with or without employment. Additionally, the value of the time spent by the unemployed cannot be assumed to be less than the value of the time of the employed.[16] The unemployed, retired, and disable proportions of the study population although may not work, but their time still has equal value as any other employed person. Thus, when placing a monetary value on the study population it was important to consider this and to not treat any group differently. Given these challenges and reasons, the assumption to place the average wage salary as the monetary value of the patient's time was the best solution as it was most practical and just option.

A simplified model of productivity loss was used which included solely employee wages. The costing model did not include other measures of productivity, nor societal costs and indirect patient costs such as the psychological costs or opportunity costs. Furthermore, patient compensation resources such as health insurance model were not incorporated into the costing models. Therefore, these estimates can bias the thesis results and create

limitations to the internal validity of the cost-effectiveness analysis. Fortunately, to minimize these inaccuracies, sensitivity analysis were performed. However, to improve this thesis, a full costing evaluation of current teleglaucoma service using precise sources is recommended.

Similarly, the probabilities were derived from research literature and expert opinion and assumptions were made in order to derive the estimated probabilities. For example, the transitional probabilities assumed patients were either treated or untreated irrespectively at the same rate. That is, the probability a patient will transition to another glaucoma health state when “treated” assumed 75% patient’s compliance with treatment at all health states. Whereas “untreated” implied patients receive no treatment at all health states. Since the transitional probabilities may differ based on treatment paradigms used, uncertainties can develop. Likewise, the Markov Model probabilities are influenced by many factors. Estimates and derivations of the probabilities of each of these factors increases the likelihood of uncertainties and thus can bias the thesis results.

Lastly, the outcome measure used in the analysis was costs per QALY gained ($/QALY). Although this is a universal measure that allows standardized comparison across healthcare disciplines, it is acknowledged that there may be other useful outcome measures. “Costs per detected case” allows a more immediate measure of the direct benefits of teleglaucoma. This outcome measure can be more practical for clinicians and healthcare administrators; it is easier to understand and apply to daily clinical practice. It allows direct comparison among programs which have the same goals.[17] For future research,

it is recommended to add the “cost per detected case” measure to obtain the immediate benefits and costs to the healthcare system. Immediate outcome measures are useful for health policy decision-makers as it provides a simple decision criterion for resource allocation without the consideration of many uncertainties related to calculating long-term benefits.[17] Although, “costs per detected case” is a tangible outcome measure, unlike “$/QALY”, it excludes quality of life measures and may not capture all important benefits. Consequently, in addition to “$/QALY”, “costs per detected case” is a useful outcome measure to enhance the cost-effectiveness analysis of teleglaucoma.

5.4 Conclusions and Future Directions

In conclusion, this thesis has found teleglaucoma is more specific and less sensitive than in-person examination and it is more cost-effective screening device for glaucoma in rural populations. To optimize the results, there are several recommendations for future study directions. Future studies can examine the use of teleglaucoma in semi-urban and urban areas; its potential benefits and its cost-effectiveness. The main advantage of teleglaucoma in rural populations is the convenience and the reduction in patient travel costs. However, teleglaucoma can play a role in urban populations. Urban hospitals can be overflown with patients placing a burden on the healthcare system and prolonging patient wait times. Teleglaucoma can act to reduce patient load at the hospital and therefore, improve the efficiency of ophthalmology clinics. It is speculated that there will be cost-savings with the implementation of

teleglaucoma in urban settings, and teleglaucoma can be cost-effective in these settings as well. Direct benefits are expected from the decline of patient load at ophthalmic clinics, which translates into reduced patient wait times and minimize unnecessary ophthalmic visits. However, the cost-effectiveness in urban, cities such as Calgary or Edmonton, may not be as comparable to that of rural Alberta, because the main cost-savings found in rural areas was the reduction of patient costs due to reduced travel distances and times. In urban cities, there are more ophthalmic centers and increased access to ophthalmic care in comparison to rural areas. Thus urban patients may not have to travel as far to receive ophthalmic care. Nonetheless, urban cities are more populated than rural cities. From an economic perspective, this is beneficial as it would allow the service to reach a greater population. Consequently, future studies are needed to examine the use of teleglaucoma in urban populations and its cost-effectiveness. And when comparing implementation in either setting (urban or rural) special caution needs to be taken with regards to ethical resource allocation based on equity versus efficiency and demand versus need.

This thesis has identified gaps in literature which can help guide future studies. There is demand for randomized controlled trials on teleglaucoma to provide high quality of evidence. More comparative studies are required which analyze teleglaucoma against a comparator, specifically in-person examination, the standard of care. Future studies can examine the long term benefits of teleglaucoma. Most studies included in the thesis analysis examined the benefits of teleglaucoma directly after screening and long term benefits were not included.

Glaucoma is a chronic, progressive disease affecting the elderly and has long term consequences if not managed appropriately. Thus, more studies analyzing the long term benefits of screening are beneficial to patient outcomes.

In addition, future reviews and CEAs should examine the use of teleglaucoma systems within optometrist or pharmacist clinics. These clinics are pre-established within rural areas and are usually more abundant than ophthalmologist clinics. Placement of teleglaucoma systems within optometrist or pharmacist clinics can reduce overhead costs and essentially prove to be even more cost-effective.

5.5 Literature Cited

1. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society Evidence-based Clinical Practice Guidelines for the Management of Diabetic Retinopathy - executive summary. *Can. J. Ophthalmol.* 2012;47(2):91–6. Available: http://www.ncbi.nlm.nih.gov/pubmed/22560411. Accessed 2015 May 1.

2. Allingham, R. R., Damji K, Shields, M. B. et al. (2011). *Shields' textbook of glaucoma*. 6th ed. Philadelphia: Lippincott Williams & Wilkins.

3. Canadian Ophthalmological Society Clinical Practice Guideline Expert Committee, Delpero W, Beiko G, Casey R, et al. (2007) Canadian Ophthalmological Society evidence-based clinical practice guidelines for the periodic eye examination in adults in Canada. Can J Ophthalmol 42:39–45. doi:10.3129/can j ophthalmol.06-126e

4. Burr JM, Kilonzo M, Vale L, et al. (2007) Developing a preference-based glaucoma utility index using a discrete choice experiment. Optom Vis Sci 84, 797–808.

5. Tengs TO, Wallace A (2000) One thousand health-related quality-of-life estimates. Med Care 38, 583–637.

6. Guyatt GH, Oxman AD, Vist G, et al. (2011) GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J Clin Epidemiol 64: 407–415.

7. Guyatt GH, Oxman AD, Montori V, et al. (2011) GRADE guidelines: 5. Rating the quality of evidence-publication bias. J Clin Epidemiol 64: 1277–1282.

8. Guyatt GH, Oxman AD, Kunz R, et al. (2011) GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol 64: 1283–1293.

9. Guyatt GH, Oxman AD, Kunz R, et al. (2011) GRADE guidelines: 7. Rating the quality of evidence-inconsistency. J Clin Epidemiol 64: 1294–1302.

10. Guyatt GH, Oxman AD, Kunz R, et al. (2011) GRADE guidelines: 8. Rating the quality of evidence-indirectness. J Clin Epidemiol 64: 1303–1310.

11. Guyatt GH, Oxman AD, Sultan S, et al. (2011) GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 64: 1311–1316.

12. Guyatt G, Rennie D, Meade M, et al. (2008) Users' Guides to the Medical Literature: essentials of Evidence-Based Clinical Practice. 2nd edition (Jama & Archives Journals). McGraw-Hill. Professional.

13. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593

14. Agostino R, Sullivan L, Beiser A (2006) Introductory Applied Biostatistics. Belmont: Brooks/Cole CENGAGE Learning.

15. Drummond MF, Sculpher MJ, Torrance GW, et al. (2005) Methods for the Evaluation of Health Care Programmes, 3rd edition. Oxford University Press.

16. Grossman, M. (1999) The human capital model of the demand for health. NBER Working Paper Series, No 7078. NBER, Massachusetts, April

17. Gold, M. R. (1996). Cost-effectiveness in health and medicine. New York: Oxford University Press.

Appendix

Appendix 1: Publisher Permissions

Re: PLOS ONE Paper Published ref:_00DU0Ifis._500U0JPhu6:ref THESIS x

plosone [redacted] Apr 16

to [redacted]

Dear Ms Thomas,

Thank you for your message. PLOS ONE publishes all of the content in the articles under an open access license called "CC-BY." This license allows you to download, reuse, reprint, modify, distribute, and/or copy articles or images in PLOS journals, so long as the original creators are credited (e.g., including the article's citation and/or the image credit). Additional permissions are not required. You can read about our open access license here: http://www.plos.org/about/open-access/.

There are many ways to access our content, including HTML, XML, and PDF versions of each article. Higher resolution versions of figures can be downloaded directly from the article.

Thank you for your interest in PLOS ONE and for your continued support of the Open Access model. Please do not hesitate to be in touch with any additional questions.

Kind regards,

Laura Perry
Staff EO
PLOS ONE

Case Number: 03898592
ref:_00DU0Ifis._500U0JPhu6:ref

---------- Original Message ----------
From: Sera-Melisa Thomas [redacted]
Sent: 15/04/2015
To: [redacted]
Subject: Re: PLOS ONE Paper Published

Dear Plos One Staff,

The paper I recently published with your journal, The Effectiveness of Teleglaucoma versus In-Patient Examination for glaucoma screening: a Systematic Review and Meta-Analysis, is part of my thesis. I would like to obtain permission to use my article in my thesis. Please let me know the steps towards this.

Kindly,
Sera Thomas
--
Western University, Schulich School of Medicine and Dentistry
Ivey Eye Institute, St. Joseph's Healthcare

MSc Epidemiology Candidate 2015

Appendix 2: Systematic Review Search Strategies

DATABASE		SEARCH TERMS
OVID Medline		
	1	Exp Glaucoma/ OR Intraocular Pressure/ OR Ocular hypertension/
	2	Glaucoma* OR Intraocular pressure OR Intra-ocular pressure OR Intraocular hypertension OR Intra-ocular hypertension OR Intra-ocular tension OR Intraocular tension OR Ocular hypertension OR Ocular tension OR Eye tension OR Eye pressure
	3	1 OR 2
	4	Remote consultation/ OR Telemedicine/ OR Telepathology/ OR Mobile Health Units/ OR Community Pharmacy Services/
	5	Automated detection OR Teleglaucoma OR Telescreen* OR Teleophthalm* OR Tele-ophthalm* OR Tele-glaucoma OR Telemedicine OR Tele-medicine OR digital indirect ophthalmoscop* OR Telemonitor* OR Tele-monitor* OR Teleconsult* OR Tele-consult* OR Telediagnos* OR Tele-diagnos* OR Telehealth OR Tele-health OR Mobile health OR eHealth OR Automated Perimetry Exam*
	6	4 OR 5
	7	Diagnosis/ OR Early diagnosis/ OR Diagnostic Techniques, Ophthalmological/ OR Tonometry, Ocular/ OR Diagnosis.fs. OR Vision screening/ OR Mass screening/ OR Visual Field Tests/
	8	Diagnos* OR Screen* OR Tonomet* OR Detect* OR Perimetr* OR Campimetr* OR Visual field test* OR Oculplethysmograph* OR Vision test* OR Early diagnosis
	9	7 OR 8
	10	3 AND 6 AND 9
	RESULTS	86
		Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
OVID EBMASE		
	1	Exp glaucoma/ OR Intraocular pressure abnormality/ OR Intraocular pressure/
	2	Glaucoma* OR Intraocular pressure OR Intra-ocular pressure OR Intraocular hypertension OR Intra-ocular hypertension OR Intra-ocular tension OR Intraocular tension OR Ocular hypertension OR Ocular tension OR Eye tension OR Eye pressure
	3	1 OR 2
	4	Telemedicine/ OR Telehealth/ OR Telediagnosis/ OR Telepathology/ OR Teleconsultation/ OR Telemonitoring/ OR computer assisted perimetry/
	5	Automated detection OR Teleglaucoma OR Telescreen* OR

		Teleophthalm* OR Tele-ophthalm* OR Tele-glaucoma OR Telemedicine OR Tele-medicine OR digital indirect ophthalmoscop* OR Telemonitor* OR Tele-monitor* OR Teleconsult* OR Tele-consult* OR Telediagnos* OR Tele-diagnos* OR Telehealth OR Tele-health OR Mobile health OR eHealth OR Automated Perimetry Exam*
	6	4 OR 5
	7	diagnosis/ OR early diagnosis/ OR diagnostic accuracy/ OR diagnostic test accuracy study/ OR diagnostic value/ OR perimetry/ OR oculoplethysmography/ OR vision test/
	8	Diagnos* OR Screen* OR Tonomet* OR Detect* OR Perimetr* OR Campimetr* OR Visual field test* OR Oculplethysmograph* OR Vision test* OR Early diagnosis
	9	7 OR 8
	10	3 AND 6 AND 9
		Embase Classic+Embase 1947 to 2014 March 11
CINAHL		
	1	(MH "Glaucoma+") OR (MH "Ocular Hypertension") OR (MH "Intraocular Pressure")
	2	Glaucoma* OR Intraocular pressure OR Intra-ocular pressure OR Intraocular hypertension OR Intra-ocular hypertension OR Intra-ocular tension OR Intraocular tension OR Ocular hypertension OR Ocular tension OR Eye tension OR Eye pressure
	3	1 OR 2
	4	(MH "Telehealth") OR (MH "Telemedicine") OR (MH "Remote Consultation") OR (MH "Telepathology") OR (MH "Mobile Health Units")
	5	Automated detection OR Teleglaucoma OR Telescreen* OR Teleophthalm* OR Tele-ophthalm* OR Tele-glaucoma OR Telemedicine OR Tele-medicine OR digital indirect ophthalmoscop* OR Telemonitor* OR Tele-monitor* OR Teleconsult* OR Tele-consult* OR Telediagnos* OR Tele-diagnos* OR Telehealth OR Tele-health OR Mobile health OR eHealth OR Automated Perimetry Exam*
	6	4 OR 5
	7	(MH "Diagnosis") OR (MH "Diagnostic Services") OR (MH "Diagnosis, Eye") OR (MH "Tonometry") OR (MH "Vision Screening") OR (MH "Vision Tests") OR (MH "Perimetry") OR (MH "Early Diagnosis")
	8	Diagnos* OR Screen* OR Tonomet* OR Detect* OR Perimetr* OR Campimetr* OR Visual field test* OR Oculplethysmograph* OR Vision test* OR Early diagnosis
	9	7 OR 8
	10	3 AND 6 AND 9
Cochrane, Web of		
	1	Glaucoma* OR Intraocular pressure OR Intra-ocular pressure

Science, BIOSIS, Dissertations and Thesis, Canadian Health Research Collection		OR Intraocular hypertension OR Intra-ocular hypertension OR Intra-ocular tension OR Intraocular tension OR Ocular hypertension OR Ocular tension OR Eye tension OR Eye pressure
	2	Automated detection OR Teleglaucoma OR Telescreen* OR Teleophthalm* OR Tele-ophthalm* OR Tele-glaucoma OR Telemedicine OR Tele-medicine OR digital indirect ophthalmoscop* OR Telemonitor* OR Tele-monitor* OR Teleconsult* OR Tele-consult* OR Telediagnos* OR Tele-diagnos* OR Telehealth OR Tele-health OR Mobile health OR eHealth OR Automated Perimetry Exam*
	3	Diagnos* OR Screen* OR Tonomet* OR Detect* OR Perimetr* OR Campimetr* OR Visual field test* OR Oculplethysmograph* OR Vision test* OR Early diagnosis
	4	1 AND 2 AND 3

Footnote:

1. Thomas, Sera-Melisa; Jeyaraman, Maya; Hodge, William G.; Hutnik, Cindy; Costella, John; Malvankar-Mehta, Monali S. (2014): The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. Table_S1.docx. PLOS ONE. 10.1371/journal.pone.0113779.s001. Retrieved 16:24, Jan 20, 2015 (GMT).

Appendix 3: Hierarchical Logistic Regression Results

Refining starting values:

Iteration 0: log likelihood = -78.600767 (not concave)
Iteration 1: log likelihood = -75.982129
Iteration 2: log likelihood = -75.554028
Iteration 3: log likelihood = -75.340131

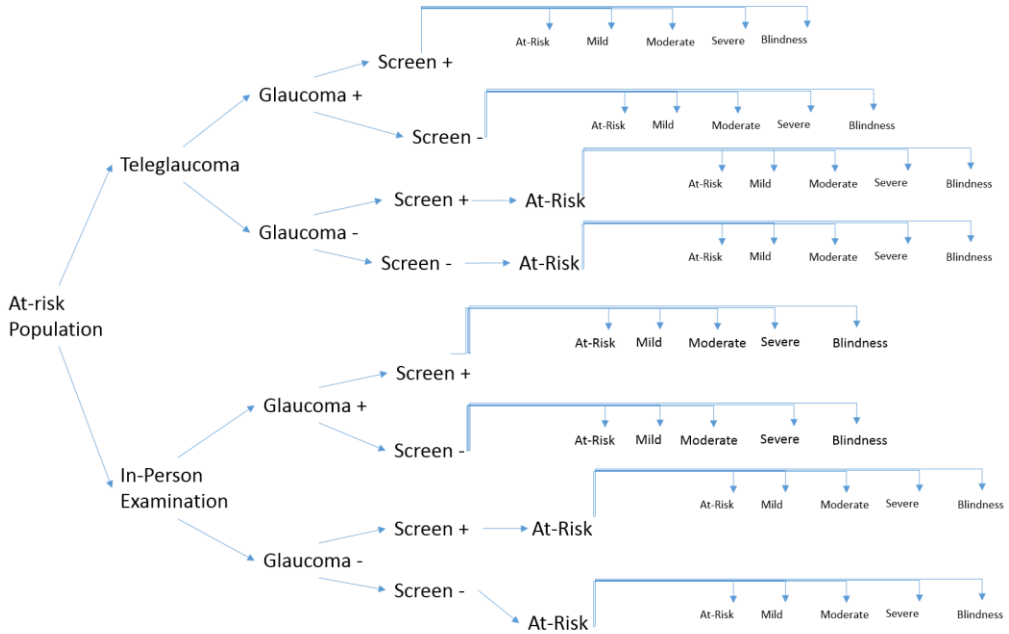
Performing gradient-based optimization:

Iteration 0: log likelihood = -75.340131
Iteration 1: log likelihood = -75.338524
Iteration 2: log likelihood = -75.338524

Meta-analysis of diagnostic accuracy
Log likelihood = -75.338524 Number of studies = 8

	Coef.	Std. Err.	z	P > |z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.603718	.2012079			1.209357	1.998078
E(logitSp)	1.327128	.3199906			.6999575	1.954298
Var(logitSe)	.2967446	.1757148			.0929718	.947141
Var(logitSp)	.9162078	.5546539			.2797007	3.001197
Corr(logits)	.485518	.3151724			-.271123	.8712955
HSROC						
Lambda	3.127015	.4806803			2.184899	4.069131
Theta	.5623328	.3130932			-.0513186	1.175984
beta	.5636856	.3954614	1.43	0.154	-.2114045	1.338776
s2alpha	1.54916	.8267713			.5442752	4.409345
s2theta	.1341308	.0918339			.0350546	.5132295
Summary pt.						
Se	.8325373	.0280522			.7701852	.8805951
Sp	.7903651	.0530186			.6681784	.8759145
DOR	18.74346	8.251661			7.908883	44.42062
LR+	3.971368	1.064445			2.348511	6.715643
LR-	.2118802	.0431373			.1421647	.3157831
1/LR-	4.719649	.960887			3.166731	7.034096
Covariance between estimates of E(logitSe) & E(logitSp) .0254672						

Appendix 4: Markov Model Decision Tree



Appendix 5: Estimated Direct Costs to Patients

Source		Unit	$/unit	Cost ($)
	Teleglaucoma			
CBC, 2014[1]	Travel distance (km)	0	$1.264/Liter*0.089L/km	0
StatsCan, 2013[2]	Travel time (hour)	0	$29.54/hr	0
	Duration of Doctor visit (hour)	1.3	$29.54/hr	38.40
	Absence from work (hour)	3.3	$29.54/hr	97.48
			TOTAL	135.88
	In-person Care			
CBC, 2014[1]	Travel distance (km)	4906	$1.264/Liter x0.089L/km	551.90
StatsCan, 2013[2]	Travel time (hour)	61.23	$29.54/hr	1808.73
	Duration of Doctor visit (hour)	1.91	$29.54/hr	56.6
	Absence from work (hour)	6.6	$29.54/hr	194.96
			TOTAL	2612.19

Footnote:

1. Canadian Broadcasting Corporation (CBC). (2014). *Alberta Gas Prices***.** Available: http://www.cbc.ca/calgary/features/gasprices/ Accessed 2014 Mar 3.
2. Statistics Canada (StatsCan) (2014). *Earnings, average weekly, by province and territory.* Available online <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr79-eng.htm> Accessed 2014 Mar 3.

Appendix 6: Total Cost Data (Cost per patient serviced)

Cost Type	Parameters Included	Teleglaucoma	in-person	Combined Practice (Teleglaucoma + in-person)
Initial	Fixed costs	41.87	2.39	44.26
Incremental	Patient costs, service costs, labour,	855.38	57809.74	58665.12

Appendix 7: Distribution for Probabilistic Sensitivity Analysis

Index	Variable Name	Type	Param 1	Param 2	Sample Rate	Option	Help/Explanation
1	dist_cost_blind	Gamma	34.5	0.001	0		Param 1 = alpha; Param 2 = lambda
2	dist_cost_inpat_incr	Gamma	95.2	0.03	0		Param 1 = alpha; Param 2 = lambda
3	dist_cost_inpat_initial	Gamma	1	0.00003	0		Param 1 = alpha; Param 2 = lambda
4	dist_cost_tele_initial	Gamma	99.2	0.085	0		Param 1 = alpha; Param 2 = lambda
5	dist_cost_tele_incr	Gamma	89.2	0.8	0		Param 1 = alpha; Param 2 = lambda
6	dist_probAtrisktomild_no_txt	Beta	64.2	41	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
7	dist_prob_atrisktomild_txt	Beta	75.2	45.3	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
8	dist_prob_mildtomod_txt	Beta	89.63	78.21	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
9	dist_prob_mildtomod_no_txt	Beta	88.21	165.23	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
10	dist_prob_mod2sev_no_txt	Beta	98.22	54.22	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
11	dist_prob_modtosev_txt	Beta	54	7.52	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
12	dist_prob_sev3blind_no_txt	Beta	29.336	170.253	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
13	dist_prob_sev2blind_txt	Beta	30.582	180.42	0	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters

Appendix 8: Derivation of Costs for teleglaucoma and in-person care

Cost Type	Teleglaucoma			Reference
Fixed	**Investment**	**$FIM(x100)**		Tuulonen et al, 1999[1]
	Fundus camera (1 unit)	200		
	ISDN installation (3 units)	6.5		
	Server computer (2 units for 5 years)	50		
	Software application (2 units for 5yrs)	50		
	Video slit-lamp (1 unit)	40		
	Total fixed costs	346.50		
	Write off 10 years (3%)	40.62		
	Use of teleophthalmology equipment	24.372		
	Video conference equipment	84		
	Writeoff 5 years	18.342		
	Automated perimetry – Humphrey	132		
	Write off 10 years (3%)	15.474		
	Other fixed costs			
	Service and updating	5		
	Line costs per month	3.672		
	Premise	1.608		
	Utilities	1.608		
	Other costs	7.133		
	Total other fixed costs	19.021		
	TOTAL	680.329		
	Conversion into 2014 $ CAN (x100)	8395.42		Bank of Canada, 2014[2]
		$CAN		
	Training (2 FTE Trainers, 2 weeks, at average salary in Alberta ($50K)	$4166 CAN		StatsCan, 2013[3]
	ANNUAL TOTAL	12561.42		
	Fixed Costs per examination (frequency of 300 examinations per year)	**41.8714**		Tuulonen et al, 1999[1]

Variable	**Service & staffing fees**	**$CAN/patient**		Government of Alberta Medical Procedures List 2014[4]
	Consultation	72.28		
	tonometry	25.5		
	electroencephalogram	108.57		
	interpretation	39.18		
	video	125.36		
	total	370.89		
	Additional Labour	$CAN/patient		Tuulonen et al 1999[1]
	Administrative	348.61		
	Patient Costs	$CAN/patient		
	travel	0		Thomas et al, 2014[5]
	travel time	0		Thomas et al 2014[5]
	absence from work	97.482		Tuulonen et al 1999[1]
	Cycle time	38.402		Arora et al 2014[6]
	Total	**135.884**		
Markov				
Initial	Fixed costs	$41.8714/patient		
Incremental	Patient costs, service costs & administrative labour	$855.384/patient		

Cost Type	In-patient Care			Reference
Fixed	**Investment**	**$FIM(x100)**		Tuulonen et al 1999[1]
	ISDN installation (3 units)	6.5		
	Server computer (2 units for 5 years)	50		
	Software application (2 units for 5yrs)	50		
	Total fixed costs	116.50		
	Write off 10 years (3%)	25.438		
	Use of teleophthalmology equipment	7.361		
	Video conference equipment	84		
	Writeoff 5 years	18.342		
	Other fixed costs			
	Service and updating	5		
	Line costs per month	3.672		
	Premise	3.36		
	Other costs	3.61		
	Total other fixed costs	12.032		
	TOTAL	267.283		
	Conversion into 2014 $CAN (x100)	2431.46		Bank of Canada, 2014[2]
	ANNUAL TOTAL	3298.33		
	Fixed Costs per examination (frequency of 1378 examinations per year)	**2.39**		Ng et al, 2009[7]
Variable	**Service & staffing fees**	**$CAN/patient**		Government of Alberta
	optometrist visit	65		Medical Procedures List 2014[4]
	Ophthalmic consultation	82.3		
	Neuro-ophthalmic Consult	162.6		
	total	309		
	Additional Labour	$CAN/patient	$27.37 FIM converted to 2014 CAN$	Tuulonen et al, 1999[1]
	Administrative	248.98		Bank of Canada, 2014[2]
	Patient Costs	$CAN/patient		
	travel	551.90		Thomas et al, 2014[5]
	travel time	1808.73		Thomas et al, 2014[5]
	absence from work	194.96		Tuulonen et al 1999[1]
	Cycle time	56.618		Arora et al, 2014[6]
	Total	**2612.17**		
Markov				
Initial	Fixed costs	$2.39/patient		
Incremental	Patient costs, service costs & administrative labour	$57809.73/patient		

Footnote:

1. Tuulonen A, Ohinmaa A, Alanko H, et al. (1999) The application of teleophthalmology in examining patients with glaucoma: a pilot study. J Glaucoma 8: 367–73.
2. Bank of Canada. (2014) Daily Currency Converter. Available: http://www.bankofcanada.ca/rates/exchange/daily-converter/.
3. Statistics Canada (StatsCan) (2014). Earnings, average weekly, by province and territory. Available online <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr79-eng.htm>
4. Government of Alberta (2014). Medical Procedures Lists. Available online: <http://www.health.alberta.ca/documents/SOMB-Medical-Procedures-2014-04.pdf>
5. Thomas S-M, Jeyaraman MM, Hodge WG et al. (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779. doi: 10.1371/journal.pone.0113779. pmid:25479593
6. Arora S, Rudnisky C, Damji K (2014) Improved Access and Cycle Time with an “In-house” patient-centered teleglaucoma program versus traditional in-person assessment. Telemed J E-Health 20(5):439-45.
7. Ng M, Nathoo N, Rudnisky C et al. (2009) Improving Access to Eye Care: Teleophthalmology in Alberta, Canada. J Diabetes Sci Technol 3(2): 289-296.

Appendix 9: Costs Associated with each health state

Glaucoma Stage	Costs ($/patient)	Author
0	623	Lee, 2006[1]
1	1480	
2	1765	
3	1917	
4	2464	
5	2511	

Health State	Derivative	Costs ($/patient)	Author
At-Risk	= Stage 0 costs	623	Lee, 2006[1]
Mild Glaucoma	= Stage 1 costs	1480	
Moderate Glaucoma	= Stage 2 + Stage 3 Costs	3682	
Severe Glaucoma	= Stage 4 + stage 5 costs	4975	
Blindness	= $2,613M (total costs of vision loss in Alberta) x 77,615 people with vision loss in Alberta)	33666	CNIB, 2008[2]

Footnote:

1. Lee PP, Walt JG, Doyle JJ, et al. A Multicenter, Retrospective Pilot Study of Resource Use and Costs Associated With Severity of Disease in Glaucoma. Arch Ophthalmol. 2006;124(1):12-19. doi:10.1001/archopht.124.1.12.
2. CNIB and the Canadian Ophthalmology Society. (2008) Costs of vision loss in Canada: Summary report. Available online: http://www.cnib.ca/eng/CNIB%20Document%20Library/Research/Summaryreport_Covl.pdf

Curriculum Vitae

Name:	**Sera-Melisa Thomas**
Post-secondary education and degrees:	Western University; London, Canada Master's of Science (MSc) Epidemiology 2013-2015 University of Toronto; Toronto, Canada Honours Bachelor of Science (HBSc) 2005-2009
Honours and Awards:	Translational Research Award for Best Research Paper 2015 - Canadian Glaucoma Society Western Research Open Access Fund 2014 Best Graduate Presentation – Ophthalmology Research Day 2014 Ontario Graduate Scholarship 2014-2015 Western Graduate Scholarship 2013-2015
Publications:	Thomas S-M, Jeyaraman MM, Hodge WG, Hutnik C, Costella J, Malvankar-Mehta MS (2014) The Effectiveness of Teleglaucoma versus In-Patient Examination for Glaucoma Screening: A Systematic Review and Meta-Analysis. PLoS ONE 9(12): e113779 doi: 10.1371/journal.pone.011377925479593 Thomas S-M, Hodge W, Malvankar-Mehta M (2015) The cost-effectiveness of teleglaucoma screening devices. PLoS ONE (*Under second review June 2015*).
Peer Reviewed Abstracts"	CANADIAN OPHTHALMOLOGY SOCIETY 2015 CONFERENCE: PAPER PRESENTATION. Title: The Relationship between Ophthalmic Characteristics and Utility Values of Glaucoma and Diabetic Retinopathy (DR) patients ABSTRACT PRESENTATION. Title: The Effectiveness of Telemedicine for Glaucoma Screening: Meta-Analysis & Primary Economic Analysis CSEB 2015: POSTER PRESENTATION: Title: A Cost-Effectiveness Analysis of Telemedicine for glaucoma

ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY 2015: ABSTRACT PRESENTATION Title: Utility Values associated with Ophthalmic Characteristics of Glaucoma and Diabetic Retinopathy

WESTERN RESEARCH FORUM 2015: ORAL PRESENTATION. Title: The Ethical Concerns of Teleglaucoma

LONDON HEALTH RESEARCH DAY 2015: ABSTRACT/POSTER PRESENATION. Title: A Cost-Effectiveness Analysis of Telemedicine for Glaucoma Screening

OPHTHALMOLOGY RESEARCH DAY 2014 – ST. JOSEPH'S HOSPITAL: ORAL PRESENTATION. Title: The Effectiveness of Teleglaucoma versus in-patient screening: A Systematic Review and Meta-Analysis

LONDON HEALTH RESEARCH DAY 2014: ABSTRACT/POSTER PRESENTATION. Title: Health-related quality of life of patient with glaucoma and diabetic retinopathy