Screening for glaucoma in high risk populations using the Stratus optical coherence tomography

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May 2010

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Epidemiology

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1.1 Abstract (English)

Background: Advanced imaging systems such as optical coherence tomography (OCT) can objectively measure both retinal nerve fiber layer thickness and optic disc contour. We aim to evaluate the validity of OCT for glaucoma screening in high risk populations.

Methods: Three hundred thirty-three volunteer participants with risk factors for glaucoma underwent imaging of the optic nerve and peripapillary nerve fiber layer using the Stratus version of the OCT. Based on an ophthalmologic examination and frequency doubling perimetry, participants were classified into 4 categories: normal, possible glaucoma, probable glaucoma and definitive glaucoma. The sensitivities, specificities, positive and negative likelihood ratios of the retinal nerve fiber layer and optic disc parameters were calculated.

Results: After excluding poor quality scans and missing data, the data of 210 right eyes were analyzed. Six right eyes had definitive glaucoma. Combining the best performing optic nerve head parameters (cup diameter or cup/disk vertical ratio or cup area) and nerve fiber layer parameters (superior average or inferior average or overall average) using AND-logic resulted in a sensitivity of 67% (95% confidence interval [CI], 24%-94%), specificity of 96% (95% CI, 92%-98%), positive likelihood ratio of 17.08 (95% CI, 7.06-41.4) and a negative likelihood ratio of 0.35 (95% CI, 0.11-1.08).

Conclusions: When adequate quality scans may be obtained, the Stratus has moderate sensitivity and high specificity for definitive glaucoma. Specificity is increased when parameters from both the optic nerve head and retinal nerve fiber layer scans are combined.

1.2 Abrégé (français)

Contexte: Des systèmes d'imagerie avancés tel que la tomographie en cohérence optique (OCT) peuvent mesurer objectivement la couche des fibres nerveuses rétiniennes péripapillaires et le contour du nerf optique. Nous voulons déterminer la validité de l' OCT pour le dépistage du glaucome dans les populations à haut risque.

Méthodes: Trois cent trent-trois participants volontaires à haut risque pour le glaucome ont subi l'imagerie du nerf optique et de la couche des fibres nerveuses avec la version Stratus de l' OCT. Basé sur un examen ophtalmique et la périmétrie à double fréquence, les participants ont été classifiés en 4 catégories: normal, glaucome possible, glaucome probable et glaucome definitif. Les sensibilités, les spécificités, les rapports de probabilité positive (*positive likelihood ratio*) et les rapports de probabilité négative (*negative likelihood ratio*) des paramètres de la couche des fibres nerveuses et du nerf optique ont été calculés.

Résultats: Les données de 210 yeux droits ont été analysées après avoir exclu les scans d'une qualité inadéquate. Six yeux droits ont été diagnostiqués avec un glaucome définitif. Lorsqu'on a combiné les paramètres du nerf optique les plus performants (diamètre de l'excavation papillaire ou la proportion verticale excavation/disque ou l'aire de l'excavation) avec les paramètres de la couche des fibres nerveuses (le quadrant supérieur ou le quadrant inférieur ou la moyenne totale) en utilisant la logique ¨ET¨, on a obtenu une sensibilité de 67% (intervalle de confiance de 95% [95% CI], 24%-94%), une spécificité de 96% (95% CI, 92%-98%), un rapport de probabilité positive (*positive*

likelihood ratio) de 17.08 (95% CI, 7.06-41.4) et un rapport de probabilité négative (*negative likelihood ratio*) de 0.35 (95% CI, 0.11-1.08).

Conclusions: Lorsque des scans d'une qualité adéquate peuvent être obtenus, le Stratus a une sensibilité modérée et une spécificité élevée pour le glaucome définitif. La spécificité est augmentée lorsque des paramètres de la couche des fibres nerveuses rétiniennes et du nerf optique sont combinés.

2.0. Contributors

2.1. Acknowledgements

I thank my supervisor, Dr. Jean-François Boivin, for his invaluable advice, suggestions for improving the scientific rigor of the project, guidance in grant applications, availability and timely feedback during the writing and re-writing process and his patience. I thank my co-supervisor, Dr. Paul Harasymowycz, for his constant advice, availability during the project, the use of the database, Bellevue clinic and access to advanced technology. I am grateful to Dr. Lawrence Joseph for his prompt replies to my numerous queries about statistical software, suggestions for improvement and reviewing the statistical methods. I greatly appreciated Dr. Alvine Kamdeu Fansi's knowledge and data sharing, organization of screening sessions and enthusiasm for glaucoma screening. I thank Katherine Hayden, Suzanne Lariviere and André-Yves Gagnon who helped me navigate the administrative aspects of the program, tracked my progress (and sometimes lack thereof) which helped me meet deadlines. Finally, I thank the Fonds de recherché en santé du Québec for their support of my degree studies and acknowledge the funding provided by Allergan Inc. for this project.

2.2 Contributing authors

Gisèle Li wrote the protocol based on previous work done by Paul Harasymowycz using another imaging device (confocal scanning laser ophthalmoscopy). She wrote the grant applications, examined 36% of patients in the database, classified eyes, planned the analyses, performed the analyses and wrote the manuscript.

Alvine Kamdeu Fansi recruited patients, coordinated screening sessions, created and maintained the database, performed the perimetries and prepared the section of the manuscript on frequency doubling perimetry in the methods section.

Jean-François Boivin evaluated the protocol, reviewed the grant applications, supervised the progress of the project in order to ensure timelines were being respected, provided critical review of results and supervised the preparation of the manuscript. He was available for discussion regarding issues pertaining to the validity and progress of the project as they arose.

Lawrence Joseph contributed software for sample size calculations of diagnostic tests and support for this software, reviewed the analyses plan and results, offered suggestions for alternate Bayesian analyses and performed sample size calculations for these alternate analyses. He also reviewed the thesis and provided suggestions for improvement.

Paul Harasymowycz developed the idea for the project and initiated the study. He examined 64% of patients in the database. He provided the imaging devices, equipment and office space for most screening sessions. He reviewed grant applications, discussed the analyses plans and provided critical appraisal of the manuscript.

3. Introduction

Glaucoma is an optic neuropathy characterized by loss of optic nerve tissue and visual field defects. It is the primary cause of irreversible blindness worldwide.[1] Detection of the disease or its progression is important for timely intervention to prevent irreversible vision loss. Unfortunately, glaucoma is asymptomatic early in the disease process. Therefore the detection of structural damage before functional vision loss occurs is highly desirable given that effective intervention to prevent glaucoma progression exists. Lowering of intraocular pressure with topical eye drops or filtration surgeries has been shown to prevent loss of visual field.[2, 3]

The earliest observable defect in glaucoma is atrophy of the retinal nerve fiber layer. [4] Loss of the disc rim in the optic nerve head has also been shown to precede visual field loss.[5, 6] Advanced imaging systems such as optical coherence tomography (OCT) can objectively measure both nerve fiber layer thickness and optic disc contour. This technology has been shown to identify structural tissue loss before functional deficits are detectable. [7]

Previous studies evaluating the Stratus for glaucoma detection have been conducted amongst eye clinic or Glaucoma Service patients.[8-10] The Stratus has not been studied for screening purposes in a study population with less severe glaucoma than found in hospitals and clinics. The sensitivity and specificity of diagnostic tests have been shown to depend on the disease spectrum in the population in which they are used.[11] Spectrum bias occurs when the study population is not representative of the target population.[11] Although the Stratus may perform well in patients with advanced glaucoma where tissue loss is severe involving the entire optic nerve head, the Stratus may not

detect as easily subtle thinning involving only the inferior rim as seen in earlier forms of glaucoma. The utility of the Stratus for screening would need to be studied in a population where most subjects are normal or have early glaucoma. The patient population followed in eye clinics or hospitals has a higher proportion of cases of advanced glaucoma compared to a population targeted by potential screening programs.

3.1 Rationale

In 1996, the Quebec Agency for Health Services and Technology Assessment issued a statement which did not support the implementation of a formal screening program for glaucoma because of the high degree of uncertainty in the literature regarding treatment benefit and the high cost of such as program.[12] Since then, evidence has emerged showing treatment to be effective at delaying the progression of glaucoma.[13] Also, new imaging devices which show promise in the early detection of glaucoma have been developed.[14] These developments have prompted a re-consideration of screening recommendations for glaucoma.[15] As there is a projected decrease in the ratio of ophthalmologists to patients in Canada over the next 20 years,[16] access to ophthalmology clinics for screening examinations will be increasingly limited. In this context, screening tests administered by non-physicians would be useful in high-risk populations.

In particular, the comparative validity of potential screening tests has become an important area of research. To our knowledge, the validity of the Stratus has not been assessed for screening.

3.2 Objectives

Our objectives are to:

1. Estimate the validity of the Stratus optical coherence tomography in a high risk screening population.
2. Identify the best performing combination of test parameters from the retinal nerve fiber layer and optic nerve head scans.

4. Glaucoma: clinical background

"Glaucoma" refers to a group of diseases that have in common a characteristic optic neuropathy with associated visual field loss for which elevated intraocular pressure is one of the primary risk factors.[17] In order to understand the classification of glaucoma and diagnostic methods, a brief review of ocular anatomy is necessary.

4.1. Ocular anatomy

The eyeball is divided into two main areas: the anterior chamber and the posterior chamber. The anterior chamber is the space between the cornea anteriorly and the iris posteriorly (Figure 1 based on drawings by Frank Netter).[18] The most peripheral part of the anterior chamber is called "the angle" because this area is defined by the geometric angle between the cornea and the iris. Within this angle lie the outflow passages for intraocular fluid. Intraocular fluid within the anterior chamber is called "aqueous humor" or "aqueous". Aqueous drains from the anterior chamber into the angle of the eye which contains a circumferential canal called the "Canal of Schlemm" (shown in cross-section on figure 1). Fluid within this canal eventually drains into episceral veins.

The posterior chamber is the area posterior to the iris and includes the lens and the vitreous body. The walls of the eyeball are composed of concentric layers. The layers (from innermost to outermost) are the retina, the choroid and the sclera.

The retina is composed of different cellular layers (Figure 2 based on figures in Ophthalmology).[19] The innermost layer consists of axons (nerve fibers) traveling together. This layer of axons forms the retinal nerve fiber layer. The cell bodies of these axons reside in the second innermost layer of the retina, the retinal ganglion cell layer.

The axons of the retinal ganglion cells join in the posterior eye wall to form the optic nerve. The optic nerve is composed of 1.2-1.5 million axons of retinal ganglion cells.[17]

Glaucoma is a disease of the optic nerve and is associated with a loss of axons histologically.[20, 21] When examining the optic nerve head (also called "optic disc") in an eye with advanced glaucoma, one can detect an increased central depression which is called "cupping" to describe the excavated tissue. This central depression is documented as the cup-to-disc ratio which signifies the proportion of the optic nerve head excavated due to loss of axons. Glaucoma can also be manifested by a thinning of the retinal nerve fiber layer which is composed of retinal ganglion cell axons. When examining the nerve fiber layer around the optic disc, loss of the usual striations indicates a loss of axons.

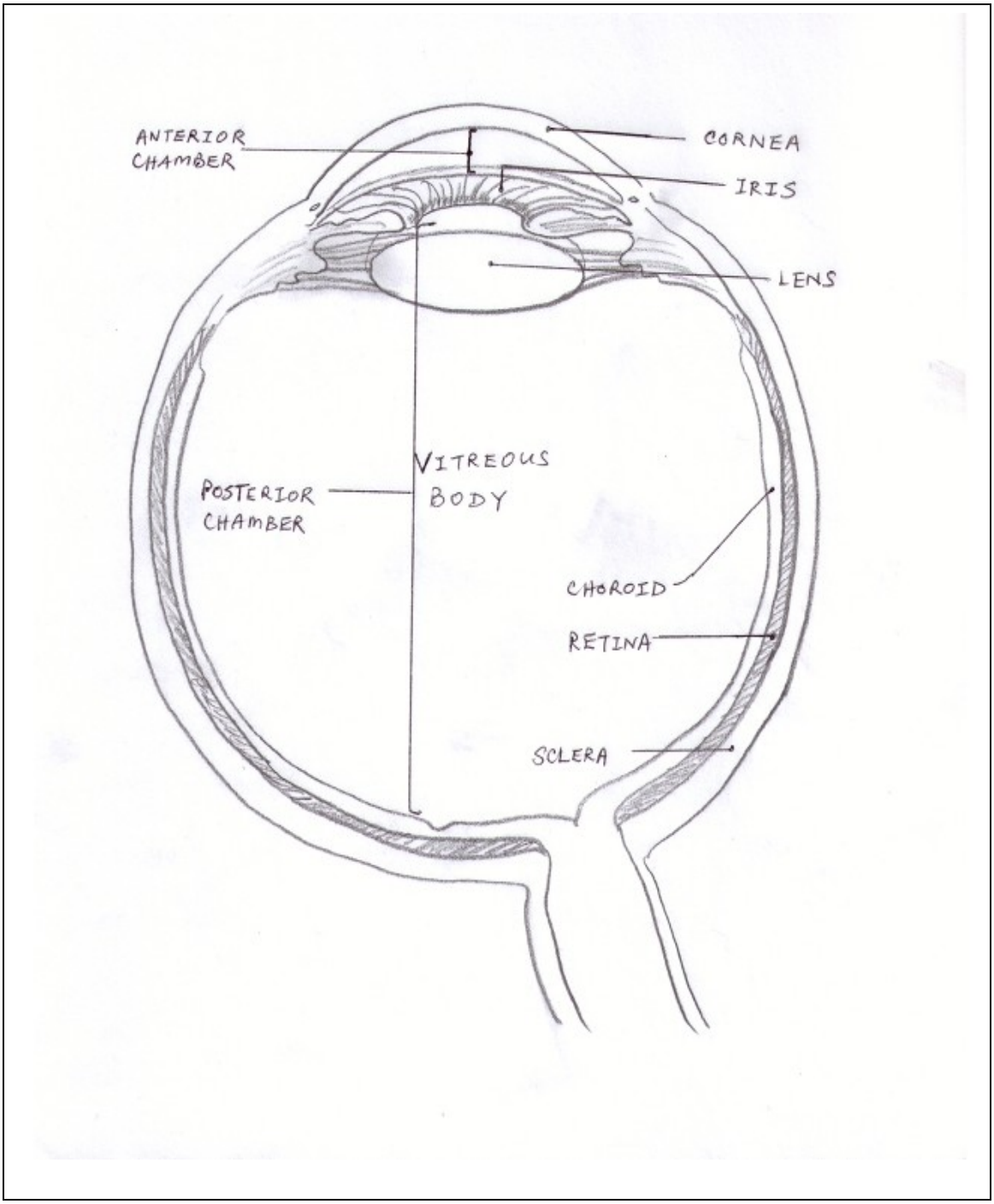


Figure 1. Ocular anatomy

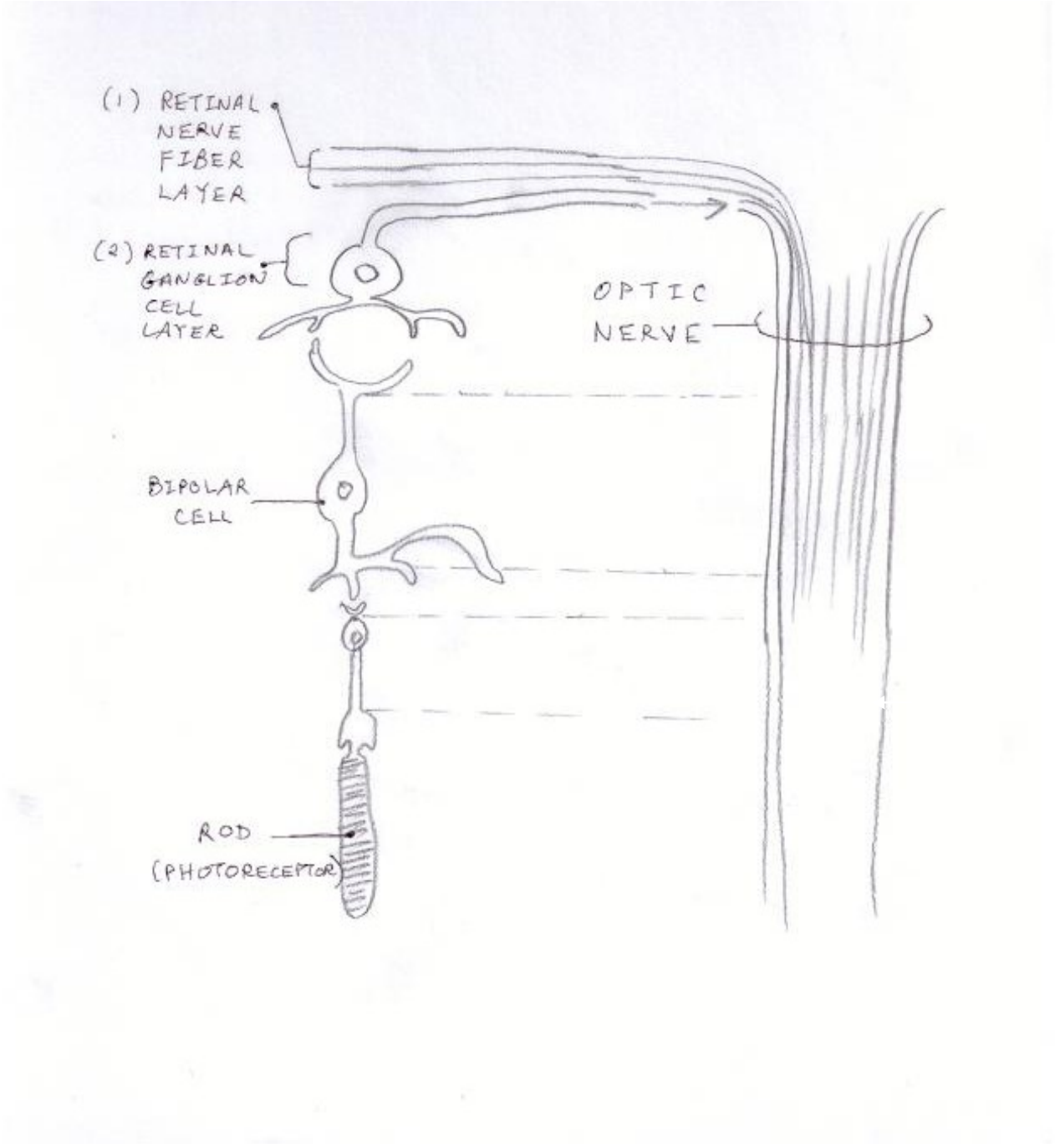


Figure 2. Retinal histology. (1) retinal nerve fiber layer (2) retinal ganglion cell layer

4.2. Diagnosing glaucoma

The critical elements of a diagnosis of glaucoma depend on the optic nerve head and peripapillary nerve fiber layer examination as well as automated visual field testing.

4.2.1. Clinical examination of the optic nerve head and retinal nerve fiber layer

The optic nerve head can be assessed clinically with a direct or indirect lens. Direct ophthalmoscopy (using a direct lens) allows for a highly magnified view (15 times) of the optic disc; however, the view is monocular and assessment of the three dimensional surface features of the optic nerve are difficult to assess as stereopsis (3-dimensional views) depends largely on binocular vision.

Most ophthalmologists generally use an indirect non-contact lens and a slit-lamp biomicroscope to visualize the optic nerve head. This indirect viewing system provides a binocular, three-dimensional view of the optic nerve head and retina. The innermost layer of the retina is the retinal nerve fiber layer. The peripapillary retinal nerve fiber layer is the part of the retinal nerve fiber layer surrounding the optic nerve. While evaluating the optic nerve, the peripapillary retinal nerve fiber layer can be assessed as well.

Typical features of glaucomatous damage are focal thinning of the disc rim, concentric atrophy, deepening of the cup, pallor/cup discrepancy, optic disc hemorrhages, peripapillary nerve fiber bundle defects.[22] Loss of axons within the retinal nerve fiber layer usually appears as dark-shaped stripes or wedge shaped defects within the normal striations of the retina.

The extent of cup deepening and rim loss is often documented using the cup-to-disc ratio. When examining the nerve with a magnifying lens and slit-lamp microscope, the examiner sees a whiter, depressed area centrally which is called the "cup". Surrounding the cup is orange tissue which is called the "rim". The cup and the encircling rim together form the disc or optic nerve. The examiner determines the cup-to-disc ratio by estimating the proportion of the disc area occupied by the central whiter tissue. Often the examiner can measure the vertical diameter of the central whiter tissue and surrounding orange tissue using the length of the slit-lamp light beam to help quantify this clinical estimate. However, this summary ratio does not adequately describe focal areas of thinning nor does it take into account the disc size which may influence the clinical interpretation of the cup-to-disc ratio. For example, a large cup-to-disc ratio may be normal in a large disc in the same way that a large doughnut would be expected to have a bigger hole than a smaller doughnut. However, a large cup-to-disc ratio implies a significant loss of rim tissue in a small disc. The Disc Diameter Likelihood Score addresses these limitations of the cup-to-disc ratio notation. The disc can be scored from 0-7 with higher numbers representing more advanced stages of glaucoma. Each score is associated with 3 standard drawings: one drawing for each category of disc size (small, normal or large disc).[23] The Diameter Likelihood Score is a more comprehensive method to document the optic nerve head exam.

The single most useful feature from the optic nerve examination for detecting glaucoma is the vertical cup-to-disc ratio when associated with a visual field defect.[24] In Europeans, the 97.5 percentile is typically associated with a vertical cup-to-disc ratio of 0.7.[25] However, optic disc parameters such as size vary amongst different ethnic groups.[26]

Small discs with small cups are potentially pathological while large discs with large cups may be normal. The separation between normal and abnormal for optic disc parameters is not clear. The diagnostic accuracy of one parameter from the optic nerve examination in isolation is inadequate for screening while a combination of parameters improves sensitivity and specificity.[27] However, a detailed optic nerve head examination requires an experienced observer.

4.2.2. Subtypes of glaucoma

Although the diagnosis of glaucoma is made based on the examination of posterior ocular structures (optic nerve head and retinal nerve fiber layer), the examination of anterior structures is important for determining the subtype of glaucoma. Glaucoma has been classified into subtypes based on the appearance of the angle which can be opened or closed. The angle is described as "open" when the outflow structures between the cornea and iris can be visualized during the ocular examination. Alternatively, when no outflow structures can be seen, the angle is described as "closed". The 2 main subtypes of glaucoma are open angle glaucoma and angle-closure glaucoma. Classification into open angle and angle closure is important from a therapeutic perspective. Open angle glaucoma is usually initially treated with eye drops and is considered a chronic disease whereas angle closure glaucoma may present as an acute ocular emergency requiring an immediate laser procedure to enable aqueous outflow. Our study focuses on open angle glaucoma.

Open angle glaucoma has been subdivided into primary and secondary forms. Primary open angle glaucoma is defined by an absence of any anatomically identifiable

cause leading to outflow obstruction and elevation of intraocular pressure. The etiology is considered to be an abnormality in the meshwork overlying the Canal of Schlemm. Glaucoma is considered secondary when an abnormality is identified which leads to the intraocular pressure elevation. For example, an iris tumor which blocks the canal of Schlemm and causes raised intraocular pressure would be considered a secondary open angle glaucoma. As knowledge of the pathophysiology underlying glaucoma expands, the primary/secondary scheme has become less relevant.[17] Our study focuses on primary-open angle glaucoma and the term "glaucoma" will be used to refer to primary open angle glaucoma in this text.

4.2.3. Visual field tests

Standard automated perimetry is considered to be the standard visual field test and is the most widely used perimeter in North America. Patients are shown a light stimulus at pre-set test locations within the visual field. The light is progressively dimmed or brightened in a stepwise fashion to identify the threshold at which detection occurs. The thresholds for the different areas of the field are compared to those of an age-matched database. The examination usually covers the central 30º or 24º which are most clinically relevant.[28] In a recent meta-analysis and systematic review of screening tests for open angle glaucoma, standard automated perimetry had a sensitivity of 73% (95% credible interval, 28 to 95) and a specificity of 64% (95% credible interval, 22 to 92) when only higher quality studies were included.[14]

Another type of visual field test can be done with frequency doubling technology which uses an alternating grey-white grating pattern instead of a light stimulus. The

advantages include portability, shorter testing times and lack of interference from uncorrected refractive errors.[29] Frequency doubling technology may detect functional loss up to 4 years earlier than standard automated perimetry by stimulating the magnocellular pathway, the ganglion cell pathway thought to be damaged early in glaucoma.[30, 31] Depending on how an abnormal test is defined, frequency doubling technology has a sensitivity and specificity above 90% and may have a role in screening.[32, 33]

4.3. Treatment

Treatment of glaucoma consists of lowering intraocular pressure. Intraocular pressure reduction may be achieved using topical medications (eye drops), lasers which stimulate aqueous outflow or filtration surgeries to promote aqueous drainage.[17] The effectiveness of treatment will be discussed in section 5.3.1.2.

5. Epidemiology of glaucoma

5.1. Prevalence

The case definition of glaucoma varies and the clinical classification of glaucoma remains inconsistent between studies.[24] Therefore it is difficult to directly compare studies, but a growing consensus regarding diagnosis has emerged based on typical optic nerve head changes, progressive nerve damage and visual dysfunction.

Glaucoma is the primary cause of irreversible blindness worldwide affecting 67 million people.[1] In the United States, over 2 million citizens were estimated to be affected in 2000 and the number affected is projected to increase to 3.6 million by 2020 as the population ages.[34]

The prevalence of glaucoma increases with age. In developed countries, the prevalence is 2% in those over 40 years old and approximately 8% in those over 80 years old.[35, 36] The prevalence also varies with race and may be as high as 15% in those of African origin.[37] The following table (Table 1) summarizes the results of prevalence studies of primary open angle glaucoma in different populations.[38] With demographic shifts influenced by the ageing of the baby boomers, the number of individuals affected by glaucoma will increase. It is estimated that in 2010 almost 60.5 million people will be affected worldwide and this number will rise to 79.6 million in 2020.[1]

Table 1. Prevalence of primary open angle glaucoma in different populations

Etude (Année)	Groupe d'âge	*N*	Méthodes de dépistage	Critères diagnostiques	Examen du champ visuel : méthode de dépistage (%)	N[bre] de cas	Prévalence brute
Framingham, MA (1973-1975)[38]	52-85	2 433	A, T, O	DGCV	Non mentionné	28	1,4
Roscommon, Irlande (1990)[35]	≥50	2 186	A, T, G, O, P	DGCV, PIO, C/D	55,8	41	1,9
Casteldaccia, Italie[37] (avant 1992)	≥40	1 062	A, T, LF, O	DGCV	Non mentionné	13	1,2
Ponza, Italie[34] (1986)	≥40	1 034	A, O, LF, T, G	DGCV et un de PIO, C/D	55,0	26	2,5
Beaver Dam, WI[30] (1988-1990)	43-84	4 926	P, LF, T, A, O	2 anomalies de DGCV, PIO, C/D, A, C	100,0	104	2,1
Baltimore, MD[43-45] (1985-1988)	≥40 Blancs Noirs	5 308 2 913 2 395	P, T, LF, G, A, O	DGCV, LTNO ou LCFN pour les sujets non soumis à une périmétrie	100,0	132 32 100	2,5 1,1 4,2
Barbade[39] (1988-1992)	40-84, AA	4 631	P, T, LF, O, Photo du fond d'oeil	DGCV + C/D≥0,7 ou entaille de la bordure neurorétinienne	95,0	309	6,7
Sainte-Lucie[40]	≥30	1 679	T, O, P toutes les 3[e] personnes	DGCV ou PIO≥ 30 mmHg, C/D≥0,7 C/D asymétrie≥0,2	31,0	147	8,8
Japon[42] (1988-1989)	≥40	8 126	T, LF, G, Photo du fond d'œil	PIO≥21 mm Hg, DGCV, LCFN	0,0	213	2,6
Mongolie[36] (1995)	≥40	942	P, LF, G	DGCV + LTNO	100,0	5	0,5
Mamre, Afrique du Sud[41] (1992)	≥40	987	LF, G, O, T, P	DGCV + LTNO	Non mentionné	15	1,5
Australie[31] (1992-1994)	≥49	3 654	T, P, G	A, DGCV + amincissement du disque optique et C/D	Non mentionné	108	3,0

A = Antécédents
AA = Afro-Antillais
C = Chirurgie
C/D = Rapport «cup-disc»
DGCV = Déficits glaucomateux du champ visuel
G = Gonioscopie
LCFN = Lésions de la souche de fibres nerveuses
LF = Examen avec lampe à fente
LTNO = Lésions de la tête du nerf optique
O = Examen ophtalmologique
P = Périmétrie
PIO = Pression intraoculaire
T = Tonométrie

In Canada, glaucoma is the second most common cause of blindness (best-corrected visual acuity ≤20/200 or visual field <20º in the better seeing eye) amongst Canadian seniors (those over the age of 65) and affects 7% of them.[39, 40] These estimates are based on self-reports and are likely underestimates as 50% of those with glaucoma are unaware they have the disease at the time of diagnosis.[39] The burden of disease will likely increase over the next few decades as the population ages. In 2006, 13% of Canadians were 65 years of age or older. By 2026, seniors will comprise 21% of the Canadian population.[41]

In Quebec, the number of individuals suffering from primary open angle glaucoma has been estimated at 68,000 based on extrapolations of international data.[15]

5.2. Incidence

Incidence is the rate at which new cases occur during a specified period. Incidence is influenced by age and race. Estimates from population based cohort studies such as the Melbourne Visual Impairment Project showed an overall incidence of open angle glaucoma in whites aged 40 years or older to be 0.5% over 5 years. In the Barbados Eye Study, blacks of the same age had an incidence of 2.2% over 4 years.[42-44]

5.3. Risk factors

5.3.1. Intraocular pressure

Intraocular pressure (IOP) is the main modifiable risk factor for glaucoma. Most standard glaucoma treatments aim to lower IOP. The IOP in the population follows a normal distribution with the mean pressure measuring approximately 15-16 mm Hg with a standard deviation of 2.5-2.8 mm Hg.[36, 45-47] Amongst clinicians, the upper limit of a normal IOP is generally considered to be 22 mm Hg. However, the overlap in IOP between those with and without glaucoma is marked. Screening by tonometry would miss approximately 50% of all patients with glaucoma.[48] Amongst glaucomatous eyes, as many as 30-50% have normal IOPs.[17] These eyes have optic nerve damage similar to those with raised IOP. Changing the cutoff IOP for detection of glaucoma would not improve the sensitivity of tonometry as these eyes would be missed regardless of the cutoff used.

5.3.1.1. Effectiveness of treatment

Based on recent evidence, it is generally accepted that IOP reduction delays the development of visual field loss. The Early Manifest Glaucoma Trial (EMGT) was a prospective randomized trial of treatment versus no treatment to evaluate the effectiveness of IOP reduction in early, previously untreated glaucoma. “Early glaucoma” was defined according to the mean deviation. Visual field printouts provide statistical summary measures using decibel units. One summary measure is the “mean deviation” which shows how much on average the whole field departs from normal. “Decibel” is a relative term which refers to the log units of attenuation of the maximum light intensity

available in the perimeter being used.[17] A healthy eye can detect a very dim light, or a very attenuated light stimulus. For a healthy eye, the mean deviation would be close to zero because there would be almost no difference between the attenuation of the light stimulus seen by the healthy eye compared to that of the control eyes in the normative database. An eye with advanced glaucoma would have trouble seeing dimmer lights. The difference in light intensity seen by the glaucomatous eye and a normal eye would be large and, after statistical calculations performed by the visual field machine, the mean deviation would be negative. Only eyes with a mean deviation greater than -16 decibels were included in the EMGT. The study only included eyes with mild or moderate visual field loss. In the EMGT, a 25% decrease of IOP from baseline and a maximum absolute level of 25 mm Hg reduced the risk of progression at 10 years.[3, 49] More specifically, the EMGT showed the mean rate of progression at 10 yrs to be 6.0 decibels in the untreated eyes compared to 3.60 decibels in the treated eyes.[3] In other words, the EMGT showed a greater loss in the ability to detect dimmer light stimuli (as measured in decibels) in untreated eyes compared to treated eyes.

In the Advanced Glaucoma Intervention Study, eyes with an average IOP greater than 17.5 mm Hg over the first three visits (at 6 month intervals) showed a significantly greater visual field deterioration compared to eyes with IOP less than 14 mm Hg in the same time period. The amount of deterioration increased with longer follow up time.[2] Even in glaucomatous eyes with normal IOP at baseline, further IOP reduction can be beneficial. The Collaborative Normal Tension Glaucoma Study showed 60% of untreated eyes progressed at 5 years compared to 20% of treated eyes when IOP was reduced by 30% or more.[50] Some individuals may have high IOP without any signs of glaucoma and

this condition is called “ocular hypertension”. In the Ocular Hypertension Treatment Study, a 50% risk reduction of developing primary open angle glaucoma was observed in the treated versus untreated group at 5 years. However, even in the untreated group, a large percentage (more than 90%) did not develop glaucoma over time.[51]

A meta-analysis conducted by the Agence d’évaluation des technologies et des modes d’intervention en santé (AETMIS) of the government of Quebec concluded that experts agreed that treating elevated IOP prevented the appearance of primary open angle glaucoma in a certain proportion of those treated. However, there was still controversy as to the utility of treating all those with ocular hypertension or those with risk factors only.[15]

5.3.1.2. Tonometry and central corneal thickness

The generally accepted reference for IOP measurement is the Goldman applanation tonometer which is based on the Imbert-Fick law.[52] This law states that an external force against a sphere equals the pressure in the sphere times the area flattened (applanated) by the external force. The Goldman applanation tonometer uses a biprism to depress the cornea with an adjustable force which can be converted to a pressure measurement. The validity of the Imbert-Fick law depends on the sphere being dry, perfectly flexible and infinitely thin. The sphere in the case of the eyeball is neither dry, nor perfectly flexible nor infinitely thin.[53] Modifications to the original Imbert-Fick law’s equation were made such as adding a constant and fixing the diameter of the contact area (by fixing the surface area of the Goldman applanation tonometer) at 3.06 mm^2. The validity of the modified equation also depends on a presumed central corneal thickness of

520 μm.[54] However, studies have shown the central corneal thickness to vary greatly in the population from 427-620 μm.[55] Furthermore, the Ocular Hypertension Treatment Study showed thinner corneas were an independent risk factor for developing glaucoma.[51] Therefore, IOP is now interpreted in light of the central corneal thickness with thinner corneas associated with falsely low pressure measurements and thicker corneas associated with falsely high pressure measurements.

5.3.2. Other risk factors

Other known risk factors for glaucoma are age, race and family history. The influence of gender on the development of glaucoma remains unclear.[56] The prevalence of primary open angle glaucoma rises with age. In the 40-49 age group, the prevalence is 1.5% and rises to 5.1% in the 70-79 age group.[34] Race has also been shown to be a risk factor. The Baltimore Eye Survey showed a prevalence 3-4 times higher for each age group in Blacks compared to Whites. The prevalence is also higher in Hispanics of Mexican ancestry compared to whites in the 70 year old and higher age group.[57] Individuals with a family history of glaucoma are more likely to develop the disease.[58] Having a first degree family member (parent, sibling or child) has been systematically associated with a higher risk of glaucoma.[59-61]

5.4. Natural history (course and outcomes)

5.4.1. Course

The course of glaucoma can be described according to a chronic disease model composed of 3 stages.[62]

1) Latency phase: This phase begins at the onset of glaucomatous optic nerve damage and continues until the damage is detectable.
2) Detectable preclinical phase: The point where glaucoma can be detected by testing until the disease becomes symptomatic.
3) Clinical phase: Glaucoma is usually quite advanced when symptoms such as visual field loss and perceptible decreased vision become apparent. Glaucoma is usually slowly progressive and progression may take decades before becoming symptomatic. Meanwhile some individuals never go blind while others have aggressive disease which becomes symptomatic after several years.

Recent clinical trials have provided estimates of the rate of progression without treatment. The Early Manifest Glaucoma Trial (EMGT) was a prospective randomized trial of treatment versus no treatment and as mentioned previously. The EMGT showed the mean rate of progression at 10 yrs to be 0-6.0 decibels in the untreated eyes.[3] "Decibels" are an indicator of an eye's sensitivity to a light stimulus. Progression on a visual field test can be measured in terms of the eye's loss of sensitivity to light and can be quantified in decibels. During the study, some untreated patients did not show any progression even after several years without treatment. More advanced glaucoma cases were studied in the Collaborative Normal Tension Glaucoma Study which was a multicentre, prospective randomized trial comparing treatment versus no treatment.

According to Kaplan-Meier survival analysis, amongst the untreated eyes, 60% progressed at 5 years using specific visual field criteria.[50] However, progression rates vary widely depending on how progression is defined and various visual field criteria have been used in the literature.[63, 64] The stage of glaucoma at study entry may also contribute towards differences in estimates.

5.4.2. Outcomes

The risk of blindness from glaucoma was studied in a retrospective review of patient charts in a community clinical practice. Two hundred ninety-five residents of Olmsted County, Minnesota, newly diagnosed with, and treated for, open angle glaucoma between 1965 and 1980 with a mean follow-up of 15 years participated. The 20 year risk of legal blindness was 22% in both eyes and 54% in one eye.[65] Legal blindness was defined as a corrected visual acuity of 20/200 or worse, and/or visual field constricted to 20° or less in its widest diameter. Meanwhile, using the same definition for legal blindness, the 15 year risk of blindness was evaluated in a subspecialty glaucoma clinic in Seattle, Washington in patients diagnosed since 1975.[66] The 20 year risk of blindness was 9% in both eyes and 27% in one eye. Noncompliance with treatment and worse initial visual field loss were significantly associated with development of blindness. Both studies included all newly diagnosed cases irrespective of disease severity at the time of diagnosis. However, patients with early glaucoma would be expected to have a better prognosis. Therefore, these estimates may not be applicable to an individual with early glaucoma. As there have been advances in glaucoma diagnosis, pharmacotherapy and surgical treatments, newly diagnosed patients today may fare better.

6. Costs and cost-effectiveness of glaucoma treatment

6.1. Costs of treating glaucoma

A longitudinal, retrospective Canadian study compared the costs of glaucoma care amongst different groups defined by severity of visual field defects. The mean yearly overall costs based on the use of resources (costs of physician visits, procedures, medications) was estimated at 508.88 CDN$ (2001 CDN dollars).[67] Based on this figure, the direct cost of treating glaucoma in Canada would be approximately $300 million per year. The costs of treating more severe disease were higher. The annual mean costs of treating mild disease was 408.00 CDN$ compared to 609.00 CDN$ for severe disease. More severe disease has been associated with higher costs of care in other studies as well.[12, 68, 69]

In the United States, the direct medical costs in 2004 for treating glaucoma in patients aged 40 years and older were more than 2.9$ billion.[70] As the population ages, these costs will increase.

6.2. Cost-effectiveness of treating glaucoma

A cost-effectiveness study performed in the United States comparing routine glaucoma assessment and treatment to no treatment was conducted using a computer simulation of 20 million people from age 50 years to death or age 100 years. Compared with no treatment, the incremental cost-effectiveness of routine treatment (as recommended by the American Academy of Ophthalmology Preferred Practice Patterns) was 11,000$ per QALY gained assuming optimistic efficacy.[71] The World Health Organization defined any intervention with a cost per disability-adjusted life year less

than a nation's per capita gross national product as highly cost-effective.[72] When expressed as a proportion of per capita gross domestic product (GDP), this figure represents 0.26 to 0.48 U.S. per capita gross national product (assuming optimistic and conservative efficacy respectively). The study authors concluded glaucoma treatment to be highly cost-effective.

7. Screening

7.1. Principles of screening (public health definitions)

Screening has been defined as an "examination of asymptomatic people in order to classify them as likely, or unlikely, to have the disease that is the object of screening".[73] If we assume the following model of disease,[74] we might assume that earlier detection would be beneficial in all cases of disease.

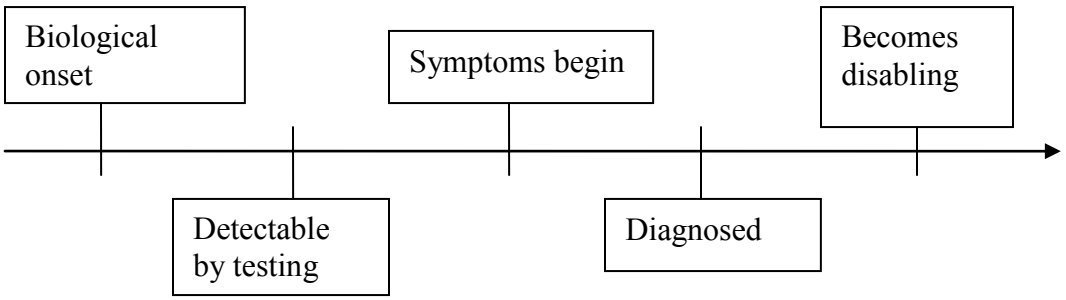


Figure 3. Model of Natural History of Diseases

However, screening may not always be beneficial, and it may sometimes be harmful or represent a disproportionate financial burden to the health care system.

In order to determine whether a disease warrants screening, the following criteria may be used.[73, 75, 76] These criteria are from Koepsell and Weiss.[74]

1. The disease is frequent or severe enough in the population that it poses an important public health problem.

2. There is a long enough time period between disease detection and symptoms for screening tests to be administered.

3. There exists effective treatment for the disease.

4. The treatment is more effective when initiated early in the course of the disease.

5. There exists a screening test for the disease which is safe, relatively inexpensive and performs well.

7.2. Public health criteria and glaucoma screening

Glaucoma fulfills all of the criteria of a disease which warrants screening.

1. Glaucoma is an important public health problem.

As discussed previously in the section on the epidemiology of glaucoma, in terms of the absolute numbers of individuals affected by glaucoma, the projected increase of those numbers associated with the ageing of the population and the importance of glaucoma as a cause of irreversible blindness relative to other eye diseases, glaucoma is an important public health problem.

2. There is a long enough time period between disease detection and symptoms for screening tests to be administered. Loss of visual function from glaucoma may be preceded by detectable structural defects (figure 4). The earliest observable defect in glaucoma is atrophy of the retinal nerve fiber layer.[4] Loss of the disc rim in the optic nerve head has also been shown to precede visual field loss.[5, 6] It has been estimated that up to 35% of nerve fibre axons may be lost before automated visual field losses become

detectable.[77] Glaucoma progression is usually on the scale of years. Progression on visual field has been found to occur over 1-5 years.[78] Progression as measured by thinning of the retinal nerve fiber layer is likely to also occur on the scale of years. A linear model was found which could relate thinning of the nerve fiber layer to losses of sensitivity on standard automated perimetry.[79]

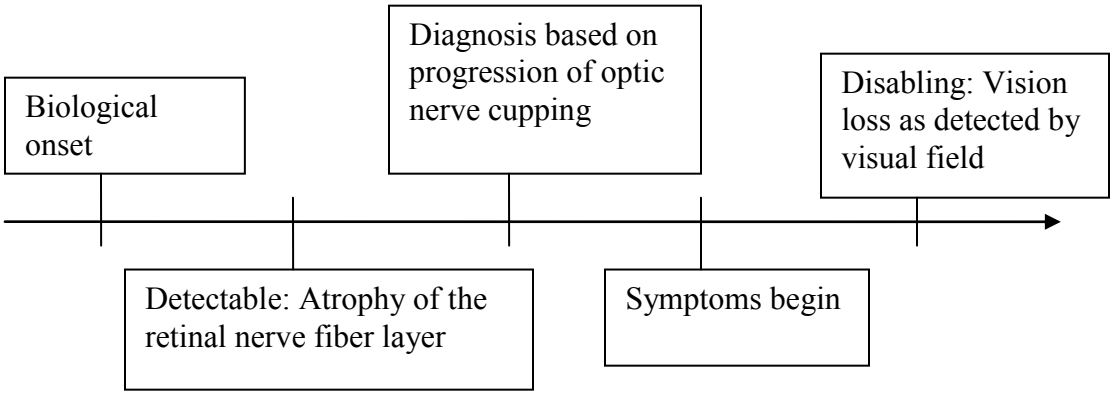


Figure 4. Model of Natural History of Glaucoma

3. There exists effective treatment for the disease. Randomized clinical trials have shown that lowering of IOP with topical eye drops or filtration surgeries can prevent loss of visual field.[2, 3]

4. The treatment is more effective when initiated early in the course of the disease. Early treatment has been shown to reduce the incidence of visual field loss.[3] As mentioned previously, the Early Manifest Glaucoma Trial included eyes with early or moderate visual field loss. The risk of progression was less with a larger initial IOP drop induced by treatment. The IOP level maintained throughout was related to initial IOP drop. The risk of progression decreased 10% with each mm Hg IOP reduction from baseline to follow-up visits. From this data, one may indirectly infer that a reduction in IOP earlier

in the course of the disease might decrease visual field progression over a lifetime more effectively than if the treatment had been initiated later.[3]

5. There exists a screening test for the disease which is safe, relatively inexpensive and performs well. Due to recent advances in imaging technology and automated perimetry techniques, there are now multiple perimetric and imaging devices being evaluated for glaucoma screening. Our study focuses on an imaging device, the Stratus. Ocular imaging devices are non-invasive and involve scanning the eye with a laser light source. The safety of lasers are classified by the United States Food and Drug Administration. Ocular imaging devices use Class I lasers which means the laser light is safe under all conditions of normal use.[80] This class includes high power lasers within an enclosure that prevents exposure to radiation and cannot be opened without shutting down the laser.[81] The Stratus costs approximately 40,000 to 45,000 USD. Other imaging devices such as confocal scanning laser ophthalmoscopy or scanning laser polarimetry cost approximately 20,000 to 30,000 USD. These devices will be discussed in section 8. The performance of these devices depend upon the gold standard for diagnosis used as well as the definitions of abnormality on the tests.

7.3. Canadian ophthalmology human resources

According to a manpower projection using the Canadian Medical Association Physician Resource Evaluation Template, the ratio of ophthalmologists (full-time equivalents) to 100,000 people within the population will be decreasing over the next 2 decades from 2.89 in 2008 to 2.47 in 2021.[16] The supply required for good medical eye care as determined by Anderson et al.[82] was 1:28 000 which is consistent with the ratio in

other developed countries.[83] The projected ratio in Canada for 2021 is 1:32 614. Most ophthalmology services are directed at the elderly and the supply of ophthalmologists is growing more slowly than this segment of the population.[16] As access to an ophthalmologist becomes more difficult, visits will become reserved for those requiring treatment of existing ocular disorders with less time available for screening.

In this context, screening tests administered by non-physicians would be useful to decrease unnecessary ophthalmology visits and allow for more efficient use of ophthalmology resources.

7.4. Cost-effectiveness of screening for glaucoma

A meta-analysis on screening for glaucoma identified 3 cost-effectiveness studies on the topic.[84]

Firstly, in 1983, Gottlieb et al. published their study following a hypothetical patient sample of one million Americans aged 40 years and older.[85] The target population included the general population, African Americans, diabetics and first-degree relatives of individuals with glaucoma. The most cost-effective screening tests varied depending on the age group. Tonometry was the only cost-effective option for subjects less than 50 years of age; however, amongst subjects in the 50-79 year age group, ophthalmoscopy was more cost-effective as the higher prevalence of glaucoma outweighed the need for identifying those with ocular hypertension.

Secondly, in 1996, Boivin et al. published a report for the government of Quebec to determine the cost-effectivness of a program that would be offered to the Quebec population aged 40 to 79 (in 1991, 2,670,210 people).[12] Scenarios based on screening that

targeted the population from 40 to 79 years of age, every three years, with a participation rate of 75%, therapeutic compliance of 75% and a treatment efficacy of 50%, led to cost-effectiveness ratios of around 100,000 CDN$ per year of blindness prevented. The report concluded that this type of program would be very costly compared to other potential health benefits that could be derived from the same resources. Their analyses did not support formal glaucoma screening program in Quebec.

Thirdly, in 1997, Tuck and Crick published a government report for the population of the United Kingdom where tonometry, ophthalmoscopy and perimetry were assessed.[86] The most cost-effective option was found to be a combination of tonometry, perimetry and ophthalmoscopy in high risk patients. The cost per true positive was approximately 850 CDN$ with the requirement of 80% minimum sensitivity.

Since then, with the advent of newer diagnostic tests for glaucoma and advances in perimetry, more recent reviews have identified the need for further data on the performance of these newer diagnostic tests in order to make recommendations. In 2007, Burr et al. concluded:

"As a basis for decision-making about the desirability of adopting screening for OAG [open angle glaucoma], our judgement is that this evidence base is insufficient: the diagnostic tests and treatment interventions available for primary OAG have changed since the identified studies were conducted ..." [28]

7.5. Current recommendations

Current recommendations continue to reflect an insufficiency of evidence to support screening although the need to focus on high risk groups has been identified. The

Canadian Task Force on the Periodic Health Examination concluded: "there is at present insufficient evidence to include or exclude tonometry, fundoscopy or automated perimetry in the periodic health examination."[87] However, it was suggested that for individuals at high risk, "…a prudent recommendation would be to include periodic assessment by an ophthalmologist with access to automated perimetry."

Similarly, in 2005, the United States Preventive Services Task Force cited insufficient evidence to recommend for or against screening adults for glaucoma. There is "good evidence that screening can detect early glaucoma and that treatment is efficacious in preventing progression to more advanced visual field defects but insufficient evidence to determine thee extent to which early detection and treatment would reduce visual impairment and increase quality of life."[75] However, the Recommendation Statement acknowledged the potential benefit of screening high risk groups: "Older African Americans have a higher prevalence of glaucoma and perhaps a more rapid disease progression, and if it is shown that screening for glaucoma reduces the development of visual impairment, African Americans would likely have greater absolute benefit than whites."[88]

In the United Kingdom, a report published in 2007 to evaluate whether screening for open angle glaucoma met the United Kingdom National Screening Committee criteria concluded population screening would probably not be cost-effective, but targeted screening of high-risk groups might be. The report also suggested that: "Glaucoma detection may be improved by increasing attendance for eye examinations, and improving the performance of current testing by either refining practice or adding in a technology-based first assessment, the latter being the more cost-effective option." [28]

In this way, there seems to be a consensus on the potential usefulness of screening in high risk groups. Furthermore, as glaucoma imaging technology evolves, research into which technology would be useful as a first assessment may be useful.

7.6. Evaluating the performance of screening tests (definitions)

In order to evaluate the performance of a screening test, the following measurement parameters can be used.[74, 89]

Sensitivity: When a condition is truly present, how often does the test detect it? Below there are a+c true cases, and the test yields a positive results on a of them. The estimated sensitivity is a/(a+c).

Table 2. Data to evaluate the validity of a binary test

	Condition present	
Test result	+	-
+	a	b
-	c	d
Total	a + c	b + d
Sensitivity	= a / (a+c)	
Specificity	= d / (b+d)	

Specificity: When a condition is truly absent, how often does the test give a negative result? There are b + d true non-cases, and the test is negative on d of them. Its estimated specificity is defined as d/(b+d).

Sensitivity and specificity may depend on the distribution of severity of the disease in the population. Therefore these test properties may vary in different settings. For example,

tests may show higher sensitivity when performed in a clinic population (more patients with more advanced disease) versus in a screening population of volunteer participants (milder disease).[90] Because of this, sensitivity and specificity may depend on the spectrum of the disease in the population studied.

Receiver operating characteristic (ROC) curves

In the case of glaucoma screening tests, we are interested in a binary outcome: whether the test detects glaucoma or not. However, many of the devices being evaluated for glaucoma screening provide information about the ocular structures or visual performance that are on an ordinal or continuous scale. In order to evaluate the validity of the results, one may choose a threshold cutoff value below which the test is considered positive for glaucoma and above which the test is considered negative for the disease. For example, in the case of optical coherence tomography peripapillary nerve fiber layer measurements, there is a normative database which provides age-matched comparisons for eyes being imaged. When the nerve fiber layer measurement is thinner than the first percentile of the normative database, the measurement is considered abnormally thin or glaucomatous. When the measurement is thinner than the 5th percentile of the normative database, the measurement is considered borderline. Sensitivities and specificities are then calculated using those cutoffs. Consequently, sensitivities and specificities will depend upon the cutoffs selected.[89] An ROC curve is a plot of sensitivity (x-axis) against 1- specificity (y-axis) for all possible cutoff values.[91] The more accurate a test is, the farther toward the upper left its curve falls in an ROC plot.

Area under the curve (AUC) of the ROC plot is sometimes used as a single summary measure of test accuracy to summarize test performance. An AUC of 0.5 is no better than chance. The minimum acceptable level for a test is an AUC of 0.6. A test with an AUC of 0.8 is considered good and a perfect test has an AUC equal to 1.0.[92]

Predictive values

When a screening test is used clinically, the subject's true status is unknown. Therefore once the test is performed and the results are available, we want to know the probability that the disease is truly present or absent, given a certain test result. The positive predictive value (PPV) is the probability that the disease is present given that the test is positive. Referring to table 2, PPV=a/(a+b).

The negative predictive value (NPV) is the probability that the disease is absent given that the test is negative. Referring to table 2, NPV=d/(c+d).

The predictive values are strongly dependent on the prevalence of disease in the population.[74] Another way of expressing the calculations for predictive values is:

$$PPV = \frac{\text{Sensitivity x prevalence}}{\text{Sensitivity x prevalence} + (1 - \text{Specificity}) \times (1-\text{prevalence})}$$

$$NPV = \frac{\text{Specificity x (1-prevalence)}}{(1-\text{Sensitivity}) \times \text{prevalence} + \text{Specificity x (1-prevalence)}}$$

We can see from the above expressions the influence of prevalence on the calculation of predictive values.[93]

Likelihood ratios

The likelihood ratio (LR) is the probability of test result X when the underlying condition is present, divided by the probability of test result X when the condition is absent. For a test with a binary result (Test + or Test -) the LR can be expressed as

$$LR+ = \frac{Pr(T+|C+)}{Pr(T+|C-)} = \frac{\text{Sensitivity}}{\text{1-Specificity}}$$

$$LR- = \frac{Pr(T-|C+)}{Pr(T-|C-)} = \frac{\text{1-Sensitivity}}{\text{Specificity}}$$

The LR provides a convenient way to update the probability that the disease is present once a particular test result has been obtained.

8.0. Potential screening methods for glaucoma

The following review of the literature on different screening methods for glaucoma was adapted from the doctoral thesis of Alvine Kamdeu Fansi.[38]

8.1. Tonometry

The Baltimore Eye Study showed that the sensitivity of tonometry was 47.1% for a specificity of 92.4% using a cutoff IOP of 21 mm Hg.[94] No cutoff was associated with a sensitivity-specificity combination elevated enough for use as a screening test. Another study using Schiotz tonometry (another method of IOP measurement used by non-ophthalmologists who may not have access to standard Goldman tonometry) showed tonometry to have only a 35.5% positive predictive value for glaucoma.[95]

8.2. Visual field: frequency doubling technology (FDT) perimetry

The results of studies estimating the performance of FDT perimetry for glaucoma screening have been highly variable. Sensitivities range from 7-92% for specificities of 87-93%.[96-98] The variability can be explained by the difference in cutoffs used to define test abnormality and the gold standard reference used to define glaucoma. Therefore the usefulness of FDT for glaucoma screening from the literature is unclear.

8.3. Imaging technologies other than optical coherence tomography

Advances in imaging technology have resulted in devices which produce quantitative, high resolution images of the optic nerve head and retinal nerve fiber layer. Other than optical coherence tomography, the most commonly used and widely available

commercial devices are the confocal scanning laser ophthalmoscope (HRTII or HRTIII; Heidelberg Engineering, Heidelberg, Germany) and scanning laser polarimeter (GDx-VCC; Carl Zeiss Meditec, Inc., Dublin, California).

8.3.1. Confocal scanning laser ophthalmoscopy

The confocal scanning laser ophthalmoscope is mainly used to obtain 3-dimensional topographic images of the optic disc although the device can image the adjacent nerve fiber layer as well. However, the nerve fiber layer measurements are largely influenced by optic nerve head tilt and measurements tend to be significantly different compared to those obtained using devices designed specifically for nerve fiber layer measurement.[99]

Multiple optical sections at consecutively deeper focal planes are combined to form a 3-dimensional image which consists of numerous pixels. Each pixel is associated with the height of the structure to provide topographic information. The disc margin contour is defined manually by an operator. The software calculates stereometric parameters within this contour. The HRTII, when used for situations similar to screening, has a sensitivity of 86% (95% credible interval 55 to 97) and a specificity of 89% (95% credible interval 66 to 98).[14] The newest version of the device (HRTIII) can make quantitative comparisons of the optic nerve head from visit to visit and provides non-operator dependent measurements; the results are highly reproducible.[100, 101]

8.3.2. Scanning laser polarimetry

The scanning laser polarimeter can objectively measure the nerve fiber layer based on the birefringent properties of the nerve fibers which are composed of neurotubules organized in a parallel fashion. This structural organization causes rotation of the plane of polarized light as it passes through and delays the travelling light. This phenomenon is known as "retardation" and is directly proportional to the thickness of the nerve fiber layer.[102] The commercially available scanning laser polarimeter, the GDx-VCC (Carl Zeiss Meditec Inc., Dublin, CA), showed high specificity (97%, CI unavailable), but low sensitivity (25.6%, CI unavailable) in a self-recruited high risk population using its best performing parameter, the Nerve Fiber Index (NFI).[103]

A recent systematic review and meta-analysis suggested FDT and HRTII were promising tests whereas ophthalmoscopy, standard automated perimetry and Goldmann applanation tonometry had relatively poor performance as single tests. The authors concluded that no test or group of tests were clearly superior as screening tests as the findings were based on heterogeneous data of limited quality.[14]

8.4. Optical Coherence Tomography technology and applications

8.4.1. Technology development and clinical applications

OCT was developed at the Massachusetts Institute of Technology by David Huang and colleagues in James Fujimoto's laboratory in 1991.[104] The technology was first introduced for retinal scanning in the mid-1990s. For the first time, clinicians could view *in vivo* cross-sectional images of the retina with near histologic resolution. This technology has been commercialized by Carl Zeiss, Inc. and has found widespread

applications for imaging the optic nerve, retinal nerve fiber layer, macula (central retina) and anterior segment of the eye.

8.4.2. Physical principles

OCT systems enable cross sectional views (tomography) of internal tissue structures by imaging reflected light. A near infrared wavelength (800-1400 nm) is scanned across the tissue. The time-of-flight delay of the reflected light is measured. Light reflected from deeper tissue layers will take longer to travel back and has a longer propagation delay than light traveling from more superficial layers. The amplitude of light is plotted against the delay to show tissue reflectivity at successively deeper levels. This plot is called an axial scan (A-scan). The Stratus OCT system can perform 400 A-scans/sec and these scans are used to generate axial and transverse pixel counts.[105] An optical measurement technique called low coherence interferometry uses a Michelson interferometer to divide a light beam into a reference beam and a signal beam. The reference beam is reflected from a mirror while the signal beam is backscattered from the tissue being scanned. Interferometry measures the effect of combining these two light waves. An interference signal (image) is generated by comparing the delays of signal beam reflections with the known delay of the reference beam reflection. To resolve the delay of sample reflections, the OCT system uses a light source that has a wide range of wavelengths (low coherence).

Resolution generally refers to the sharpness and clarity of an image and, in imaging systems, describes the ability of an imaging system to resolve detail. The earliest commercial OCT retinal scanners, OCT1 and OCT2, had 12 to 16 μm full-width at half-

maximum axial resolution. The Stratus (a.k.a. OCT3, Carl Zeiss Meditec, Inc., Dublin, California) has a higher resolution of 9-10 μm in tissue and permits visualization of individual retinal layers.[105] Even higher resolution is currently possible with ultrahigh-resolution OCT, which has demonstrated an axial resolution of approximately 3 μm.[106] Such high resolution allows for fine depth resolution and cross sectional views similar to those achieved with histologic sections.

8.4.3. Stratus applications in glaucoma detection

For glaucoma, Stratus has various scanning protocols to image the areas affected by glaucomatous damage.

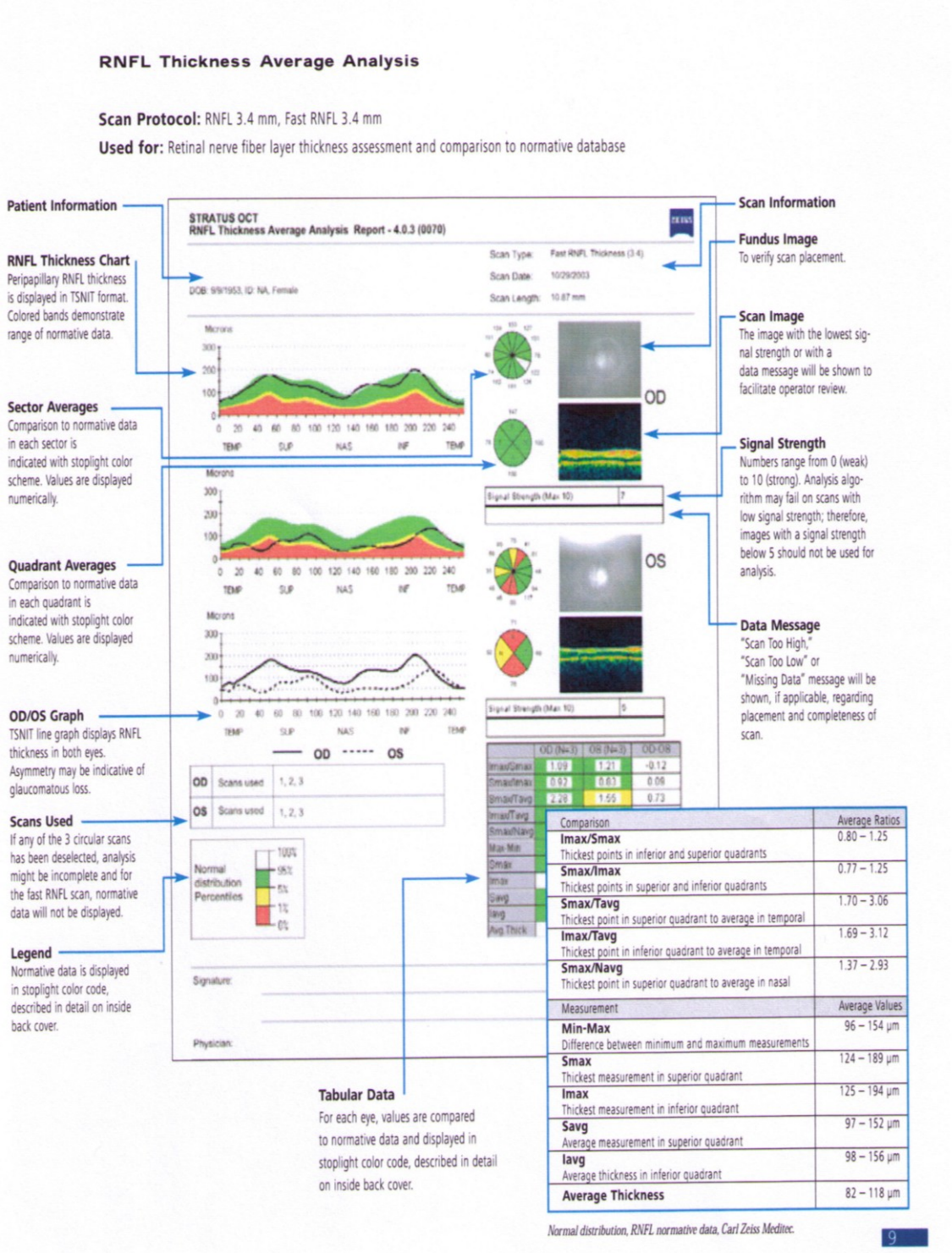


Figure 3. Stratus retinal nerve fiber layer scan

8.4.3.1. Peripapillary retinal nerve fiber layer

The Stratus performs a circular scan of 3.4 mm diameter around the optic nerve head to measure retinal nerve fiber layer thickness. The printout shows the measurements in microns as well as a comparison to age appropriate normative data (Fig. 5).[107] The Stratus nerve fiber layer thickness scanning protocol has been shown to distinguish glaucomatous eyes from normal eyes in a clinic population.[8, 108, 109] The scan provides numerous measurements including measurements of the nerve fiber layer thickness at each clock hour location and average measurements for each quadrant (superior, inferior, nasal and temporal). The most useful measurements for detecting glaucoma were found to be the overall average nerve fiber layer, the inferior and superior quadrants. These parameters were associated with area under the receiving operater curves ranging from 0.86 to 0.89.[8] In study populations with less advanced disease, ocular hypertensive eyes and those with early perimetric glaucoma were found to have statistically thinner nerve fiber layer compared to normal eyes using Stratus.[10, 110] The Stratus is currently used clinically in conjunction with an ophthalmologic examination and visual field testing for glaucoma diagnosis and follow-up. The use of Stratus nerve fiber layer scanning protocols for glaucoma screening has not been studied.

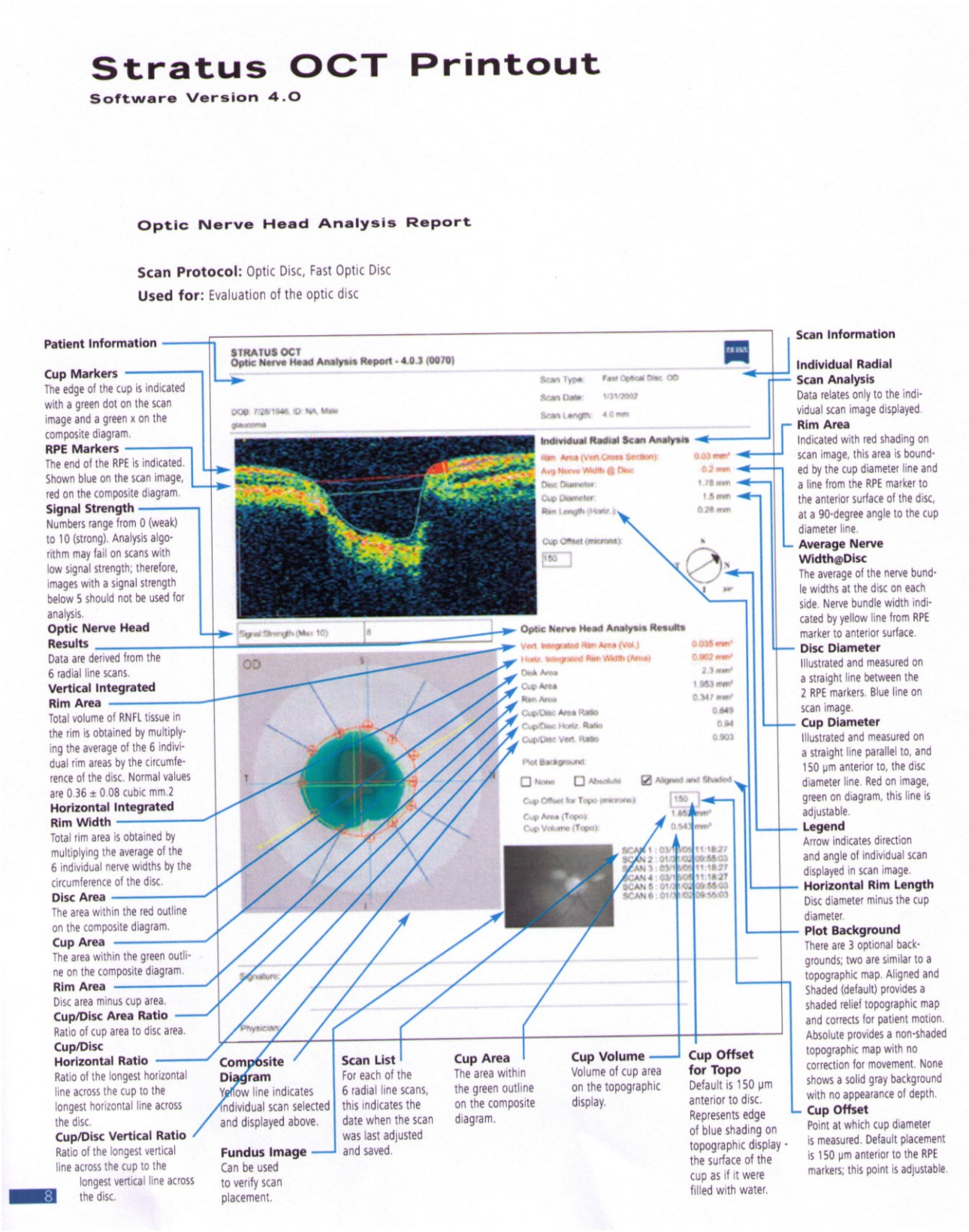


Figure 6. Stratus optic nerve head analysis report

8.4.3.2. Optic disc

During an ophthalmic examination, the appearance of the optic nerve head and peripapillary retina is the single most important feature in establishing the presence of glaucomatous damage.[111] Stratus performs optic nerve head analysis using radial line scans through the optic disc (Fig. 6).[107] In clinic populations, the best performing Stratus optic disc scan parameters were based on cup-to-disc ratios with AUC of ROC curves of 0.88.[112, 113] The Stratus optic nerve head scans are currently rarely used clinically due to the widespread use of other optic nerve head imaging devices with normative data available within these devices. The most widely used clinical optic nerve head imaging device in Canada is the Heidelberg Retinal Tomograph. Depending on the gold standard and test-positive definitions for glaucoma, sensitivity ranged from 25 to 100%, specificity ranged from 87 to 97%, positive predictive value from 28% to 68% and negative predictive value from 84% to 100%.[114] The ability to image both the nerve fiber layer and optic disc with the same machine at the same visit makes the Stratus attractive for screening purposes.

9. Manuscript

9.1 Preface

This chapter contains a published manuscript.

The contribution of each author is stated in chapter 2.

In this study, the Stratus optical coherence tomography device was used to image the optic nerve and peripapillary retinal nerve fiber layer in order to screen for glaucoma. Although the performance of the Stratus to detect glaucoma in glaucoma clinic patients is well documented, as will be discussed in the manuscript, its validity as a screening test is unknown. We have used the term "diagnostic accuracy" in the manuscript to reflect the guidelines of the Statement for Reporting Studies on Diagnostic Accuracy (Appendix 13.5) as requested by the reviewers. "Accuracy" is defined here as the degree of closeness of a measurement of a quantity to its actual value. "Precision" refers to the degree to which repeated measurements show the same results (reproducibility). In our terminology, a "valid" measurement system should be both accurate and precise.[115] As we have not performed repeated measurements, our study can correctly be regarded as a study of accuracy. To our knowledge, the use of the Stratus as a screening device in a population at high risk for glaucoma has not been previously studied.

9.2. Manuscript

10. Limitations of the study

10.1. Sampling methodology

The values calculated for sensitivity and specificity can be distorted by various factors such as the characteristics of patients included. Sampling can be defined as the process of selecting and observing a part of the population in order to make inferences about the total population.[116] To increase the probability of achieving a representative sample, the equal probability of selection method may be used whereby everyone in the sampling frame has an equal chance of being in the final sample.[116] In our study, convenience sampling was used. Subjects were selected into the sample based on convenience/availability. Convenience sampling is prone to selection bias since there may be factors associated with the availability of subjects that are related to the outcome of interest.[116] For example, less mobile and less outgoing or possibly depressed individuals would have been less likely to participate. Our study population was composed of volunteer participants who responded to offers of free screening for glaucoma. These volunteers were drawn from people in the community who responded to offers of free screening either through glaucoma screening kiosks or advertisements. Other volunteers were hospital workers and relatives or friends accompanying patients to their visits in glaucoma clinics. The inclusion criteria were the presence of one or more of the following risk factors: age over 50, of Caribbean, African or Hispanic descent, a positive family history in a first degree relative (parent, sibling, child). Our demographic data was collected by an interviewer at the time of the visit. Race was based on self-reports by the participants when asked about their ethnicity.

In order to better understand the differences between participants and non participants, we can use demographic data available for the population of Quebec from Statistics Canada.[117] Our study population had a disproportionate number of women (74.76%). In Quebec, the population between 65-74 years was 55% female. We are not aware of differences in the performance of the Stratus in men compared to women. Meanwhile, we did achieve greater participation amongst ethnic groups at risk for glaucoma compared to their representation in the Quebec population. Within the Quebec population in 2001, 6.98% were visible minorities. More specifically, 2.13% of the Quebec population was Black and 0.84% were Latin American. In our study group, 7.14% were Black and 0.95% Hispanic while 0.47% were of other visible minority groups.

10.2. Spectrum bias

Aside from demographic features, the severity of the target condition and comorbidity may influence measures of test accuracy. We have focused on earlier, asymptomatic disease with only 2.8% of subjects having definitive glaucoma. Meanwhile, the presence of comorbid conditions may result in more false-positive or false-negative test results.[11, 118] Spectrum bias may also occur if a particular comorbidity is disproportionate (either high or low) among the study population compared with the target population.[11] Co-morbid components of a disease spectrum refer to coexisting ailments, not directly related to the disease being studied study, which could yield false results. Other diseases which may cause peripapillary retinal nerve fiber layer loss and thinning include arteritic and non-arteritic optic neuropathy as well as diffuse retinal

disease. For example, optic neuropathy induces retinal nerve fiber loss to a lesser degree than glaucoma as measured by the Stratus.[119] False positive results for glaucoma are possible. We relied on the participants to volunteer information regarding their past ocular history. It is possible some study subjects actually had optic neuropathies other than glaucoma or diffuse retinal disease and had enough recovery of vision to perform the Stratus scan and were included. A more thorough record of co-morbid conditions might have been informative.

We also performed analysis to test for significant differences across subject recruitment sites for age, race, sex, glaucoma classifications, refractive error, IOP and disc area. We did not find any such differences between sites.

10.3. Excluded patients

Another limitation to the study was the number of excluded patients due to poor signal strength. Although a large number of excluded scans were performed in mobile clinics, almost one third of scans performed in the New Eye Clinic (after a part of the hospital was re-constructed at a different site) were also excluded (Table 3). This high proportion of poor quality scans may be due to inadequate maintenance of the device. The superluminescent diode of the Stratus needs to be changed regularly. As the light source becomes less intense over time, the scan quality decreases. In addition, the calibration of the device needs to be re-done regularly to ensure the mirrors are in perfect position. (Maxime Binette, representative of Zeiss, personal communication, March 12, 2010). These minute adjustments require visits from manufacturer representatives and ongoing maintenance. In the hospital, the ophthalmic photographer is responsible for

contacting the representatives. However, maintenance issues may not be prioritized given the demands of patient flow during working hours.

We assessed disease spectrum effects across sites. When the diagnostic classifications of excluded eyes (A=normal, B=possible glaucoma, C=probable glaucoma, D=definitive glaucoma) tested at different sites were analyzed (Table 4), the majority of excluded eyes were normal eyes. Of excluded eyes, approximately 2% had definitive glaucoma. The disease spectrum was similar to that of included eyes (approximately 2% having definitive glaucoma). Only at the Glaucoma Institute were a higher proportion of eyes with possible glaucoma excluded. However, the category of glaucoma used as the diagnostic standard in our manuscript was definitive glaucoma. Therefore, we do not believe spectrum distribution of the excluded eyes had a significant impact on the results.

Table 3. Quality of retinal nerve fiber layer scan per site (Right eye, n=303)

Site	Frequency (row %)		Total
	Poor quality	Good quality	
Mobile unit	35 (72.9)	13 (27.1)	48 (100.0)
New Eye Clinic (CSA)	21 (27.3)	56 (72.7)	77 (100.0)
Rosemont	26 (51.0)	25 (49.0)	51 (100.0)
Glaucoma Institute of Montreal	17 (13.4)	110 (86.6)	127 (100.0)
Total	99 (32.7)	204 (67.3)	303 (100.0)

Mobile unit: scans performed in a mobile screening unit
CSA: Centre de santé ambulatoire (a newly constructed ambulatory care centre which housed a new Eye Clinic and opened in 2006). The CSA is attached to the Maisonneuve-Rosemont Hospital.
Rosemont: The pavilion of Maisonneuve-Rosemont Hospital where the Eye Clinic was located prior to 2006.
Glaucoma Institute of Montreal: ophthalmology office/clinic outside the hospital

Table 4. Distribution of poor quality scans according to site and diagnostic classifications (Right eye, n=99)

Site	Diagnostic classification				Total
	A	B	C	D	
Mobile unit	24 (68.57%)	10 (28.57%)	1 (2.86%)	0 (0.00%)	35 (100%)
New Eye Clinic (CSA)	13 (61.90%)	5 (23.81%)	2 (9.52%)	1 (4.76%)	21 (100%)
Rosemont	17 (65.38%)	7 (26.92%)	1 (3.85%)	1 (3.85%)	26 (100%)
Glaucoma Institute of Montreal	8 (47.06%)	7 (41.18%)	2 (11.76%)	0 (0.00%)	17 (100%)
Total	62 (62.63%)	29 (29.29%)	6 (6.06%)	2 (2.02%)	99 (100%)

Pearson chi2(9)=5.8599 Pr=0.754 No significant difference

We also analyzed the characteristics of excluded patients and eyes (Table 5). There was a higher proportion of Black patients amongst those excluded as mentioned and discussed in the manuscript. Other characteristics amongst included and excluded eyes were similar (manuscript Table 2).

There were also subjects who were excluded because of a missing visual field or scans. These were missing because of the absence of one of the ophthalmic photographers who had to leave during a screening clinic because of illness. Most patients were able to return another day to perform the tests and complete the study protocol, but others did not return. These subjects had been seen by the ophthalmologist and were told their optic nerve exam was normal and likely felt they did not need to return for further testing. Another time, the visual field machine was not available and patients were re-scheduled.

Table 5. Characteristics of excluded patients and eyes (Right eye, n=99)

Demographics	
Mean age ±SD (years) Age range (years)	60.95 ± 11.50 22 to 87
Female Male	67 (67.68%) 32 (32.32%)
Race Black White	 16 (16.16%) 83 (83.84%)
Positive family history for glaucoma	30 (30.30%)
Ocular characteristics	
Mean IOP±SD (mm Hg)	16.69 ± 3.24
Mean refractive error (spherical equivalent) ± SD (Diopters) Range (Diopters) Mean disc area (mm^2) ± SD (mm^2) Range (mm^2)	-0.25 ± 2.50 -10.50 to +5.50 2.43 0.54 1.37 to 4.18
IOP=IOP; SD=standard deviation	

10.4. Gold Standard for glaucoma diagnosis

The performance of the diagnostic test depends on the criterion standard or "gold standard" selected for comparison. We initially used 4 diagnostic classifications: normal, possible, probable and definitive glaucoma (Manuscript table 1).

Manuscript Table 1. Diagnostic classifications based on clinical examination and FDT

Diagnostic classification	Examination results	
	Ophthalmic examination	FDT
A = Normal	Normal	Normal
B = Possible glaucoma	Normal	Abnormal
	Glaucoma suspect	Normal
C = Probable glaucoma	Glaucoma suspect	Abnormal
	Glaucoma	Normal
D = Definitive glaucoma	Glaucoma	Abnormal

FDT=frequency doubling technology

We finally selected "definitive glaucoma" as the gold standard which we defined as optic nerve rim atrophy with a compatible visual field defect. This standard is consistent with the widely used gold standard of perimetric glaucoma (glaucoma with optic nerve damage on stereophotographs and compatible visual field defects) and which is the standard in the ongoing Advanced Imaging for Glaucoma Study funded by the National Eye Institute in the United States.[120] This standard was also selected because reviewers of the manuscript deemed the presentation of multiple gold standards confusing for the reader. This choice may, however, introduce spectrum bias. When analysis using a less advanced form of glaucoma (probable glaucoma) as the gold standard was performed, the Stratus showed lower sensitivity (Table 6).

Table 6. Performance of combined superior average, inferior average and overall retinal nerve fiber layer (RNFL) thickness parameters using OR-logic to detect glaucoma using the Stratus 5th percentile cutoff (Right eye; n=204)

Stratus classifications	Different "gold standards"			
	ABC vs D	AB vs CD	A vs BCD	A vs D
Sensitivity (95% CI)	0.67 (0.24-0.94)	0.35 (0.15-0.61)	0.23 (0.15-0.33)	0.67 (0.24-0.94)
Specificity (95% CI)	0.85 (0.79-0.90)	0.86 (0.79-0.90)	0.89 (0.81-0.94)	0.89 (0.93-1.00)
Positive predictive value	0.12 (0.04-0.29)	0.18 (0.07-0.36)	0.61 (0.42-0.77)	0.24 (0.08-0.50)
Negative predictive value	0.99 (0.95-1.00)	0.94 (0.88-0.97)	0.61 (0.53-0.68)	0.98 (0.93-1.00)
Likelihood ratio	4.55 (2.12-9.04)	2.44 (1.16-5.20)	2.07 (1.06-3.86)	6 (2.51-13.00)
Negative likelihood ratio	0.39 (0.21-1.16)	0.76 (0.58-1.07)	0.87 (0.80-0.99)	0.38 (0.20-1.12)

A=normal;B=possible glaucoma;C=probable glaucoma;D=definitive glaucoma; CI=confidence interval

Although detecting more advanced forms of the disease is more urgent in order to initiate treatment quickly, a good screening test should be also able to detect less advanced disease in order to prevent further vision loss. The Stratus alone appears unsuitable for detecting early glaucoma in the context of screening.

Another consideration regarding the gold standard was the optic nerve head classification. An optic nerve head examination may be subjective as it is based on an ophthalmologist's assessment of the optic nerve head. In 23 eyes, 2 glaucoma specialists graded the optic nerve head. The kappa coefficient for the examination was 0.78 (95% CI 0.54-1) using the categories "normal", "suspect" and "glaucoma" to classify the nerve (table 1 of manuscript). A kappa coefficient over 0.75 is generally considered to indicate excellent reproducibility, 0.4 to 0.75 is fair to good and less than 0.40 is considered poor.[89]

10.5. Selection of right eye for analyses

We randomly chose to present the analyses of the right eyes to prevent redundancy. Although statistical methods exist to account for correlated data, we considered the data easier to interpret if the eyes were analyzed separately. Furthermore, there was a consensus amongst other researchers working in the field of glaucoma imaging that eyes should be analyzed separately (personal communication, Rohit Varma MD, MPH, steering committee, Advanced Imaging for Glaucoma Study). The analysis for both the right and left eyes separately were performed although only the results of the right eye were presented. A possible issue with selecting the right eye would be a learning effect. For example, if the right eye is always scanned first, subjects may fixate better with the left eye, generating a better signal score. However, this hypothesis was not supported by the results which are generally similar (see table 7 below).

Table 7. Performance of combined superior average, inferior average and overall retinal nerve fiber layer thickness parameters using OR-logic to detect definitive glaucoma using the Stratus (Left eye; n=212)

Stratus classifications	5^{th} percentile cutoff	1^{st} percentile cutoff
Sensitivity (95% CI)	0.67 (0.22-0.96)	0.5 (0.12-0.88)
Specificity (95% CI)	0.83 (0.77-0.88)	0.91 (0.87-0.95)
Positive Likelihood ratio	3.94 (2.08-7.49)	5.75 (2.31-14.30)
Negative likelihood ratio	0.40 (0.13-1.25)	0.55 (0.25-1.22)
CI=confidence interval		

Table 8. Sensitivity, specificity and area under the receiver operating curves of Stratus optic nerve head parameters to detect definitive glaucoma (Left eye; n=212)

Optic nerve head parameter	**Cutoff for detection of definitive glaucoma**	Sensitivity (%)	Specificity (%)	AUC (95% confidence interval) os
Cup diameter	≥0.10	83.33	72.30	0.89 (0.77-1.0)
Cup/disk vertical ratio	≥0.63	83.33	70.87	0.79 (0.68-0.89)
Cup area	≥1.22	83.33	80.10	0.85 (0.76-0.94)
Cup/disk area ratio	≥0.44	83.33	73.30	0.82 (0.74-0.90)
Cup/disk horizontal ratio	≥0.69	83.33	72.30	0.82 (0.74-0.90)
Disk diameter	≥1.94	50.00	66.00	0.59 (0.37-0.80)
Disk area	≥2.29	83.33	53.80	0.75 (0.56-0.94)
Rim area	≥0.59	83.33	8.74	0.35 (0.15-0.56)
Average nerve width at disk	≥0.25	66.70	3.40	0.12 (0.00-0.26)
Horizontal integrated rim width (area)	≥1.10	66.70	0.50	0.24 (0.03-0.46)
Rim length (horizontal)	≥0.13	83.33	0.49	0.20 (0.02-0.38)
Rim area (vertical cross section)	≥0.01	83.33	0.49	0.12 (0.00-0.25)
Vertical integrated rim area (volume)	≥0.13	66.7	3.88	0.09 (0.01-0.18)
AUC=area under the receiver operating curve				

Table 9. Performance of combined cup diameter, cup area ratio optic nerve head, cup/disk area parameters to detect definitive glaucoma using OR-logic (Left eye; n=212)

	Classification using 3 optic nerve head parameters
Sensitivity (95% CI)	1.00 (0.54-1.00)
Specificity (95% CI)	0.61 (0.54-0.68)
Positive Likelihood ratio	2.56 (2.16-3.03)
Negative likelihood ratio	0
CI=confidence interval	

Table 10. Performance of combined retinal nerve fiber layer and optic nerve head parameters using AND-logic to detect definitive glaucoma (Left eye; n=212)

	Classification using 3 retinal nerve fiber layer and 3 optic nerve head parameters
Sensitivity (95% CI)	0.67 (0.22-0.96)
Specificity (95% CI)	0.94 (0.89-0.97)
Positive Likelihood ratio	10.60 (4.90-23.00)
Negative Likelihood ratio	0.36 (0.11-1.10)
A=normal;B=possible glaucoma;C=probable glaucoma;D=definitive glaucoma; CI=confidence interval	

11. Significance of the study

The results from this study show the Stratus has inadequate sensitivity to be used as a stand alone test for glaucoma screening in the community. The Stratus would be best used as an adjunct to a clinical exam and standard perimetry as in current practice. Meanwhile, a normal RNFL scan is useful to rule out definitive glaucoma given the high negative predictive value of the test.

Furthermore, when we consider the 2 scan types- RNFL and Fast Optic Disc- the latter must be used in conjunction with the RNFL scan. The Fast Optic Disc scan does not provide a normative database for comparison. The selection of a cut-off point to define abnormality is left to the user. The optimal cut-off point is variable from one eye to another and from one population to another rendering clinical use by itself impractical.

Our study has highlighted the importance of proper maintenance of the device. We have discussed these issues with our ophthalmic photographer and the hiring of additional personnel is being considered. With these results in mind, the Stratus should not be used in mobile glaucoma screening units.

Further research questions which emanate from this study are how to improve the signal score. We have shown the Stratus may generate poorer quality images in certain groups such as Black patients. The performance of the Stratus in different ethnicities should be evaluated.

In terms of policy, our study shows the Stratus is not adequate for glaucoma screening when used alone. The optimal testing algorithm for use in widespread glaucoma screening programs in high risk populations remain to be determined. Cost-

effectiveness studies would be needed in order to determine whether there may be a role for the Stratus in excluding glaucoma in some patients and precluding further testing.

12. Conclusion

We have shown the Stratus has moderate sensitivity for glaucoma and high specificity. Although, inadequate as a stand alone test for glaucoma screening, its high negative predictive value shows it may be useful in ruling out definitive glaucoma.

Limitations of our study include the use of convenience sampling, lack of information regarding ocular comorbidities and the number of excluded scans. The study population consisted of a high proportion of women and mobile Quebecers. There was an underrepresentation of co-morbid ocular disease.

The Stratus requires a high level of maintenance in order to provide adequate quality images. It is unsuitable for mobile screening clinics.

13. Appendix

13.1. Table 11. Frequently used terms from the Stratus retinal nerve fiber layer scan

RNFL	retinal nerve fiber layer
Superior average	Measurement of peripapillary retinal nerve fiber layer in the superior quadrant. This measurement is compared to a normative database. The printout provided by the manufacturer indicates when the measurement falls below the 5th and 1st percentile of measurements within the normative database.
Inferior average	Measurement of peripapillary retinal nerve fiber layer in the inferior quadrant. This measurement is compared to a normative database. The printout provided by the manufacturer indicates when the measurement falls below the 5th and 1st percentile of measurements within the normative database.
Overall average	Measurement of the overall peripapillary retinal nerve fiber layer. This measurement is compared to a normative database. The printout provided by the manufacturer indicates when the measurement falls below the 5th and 1st percentile of measurements within the normative database.

13.2. Selected areas under the curve of the receiver operating characteristic plots

Figure 7. Receiver operating characteristic plot of cup diameter to detect definitive glaucoma (Right eye; n=209)

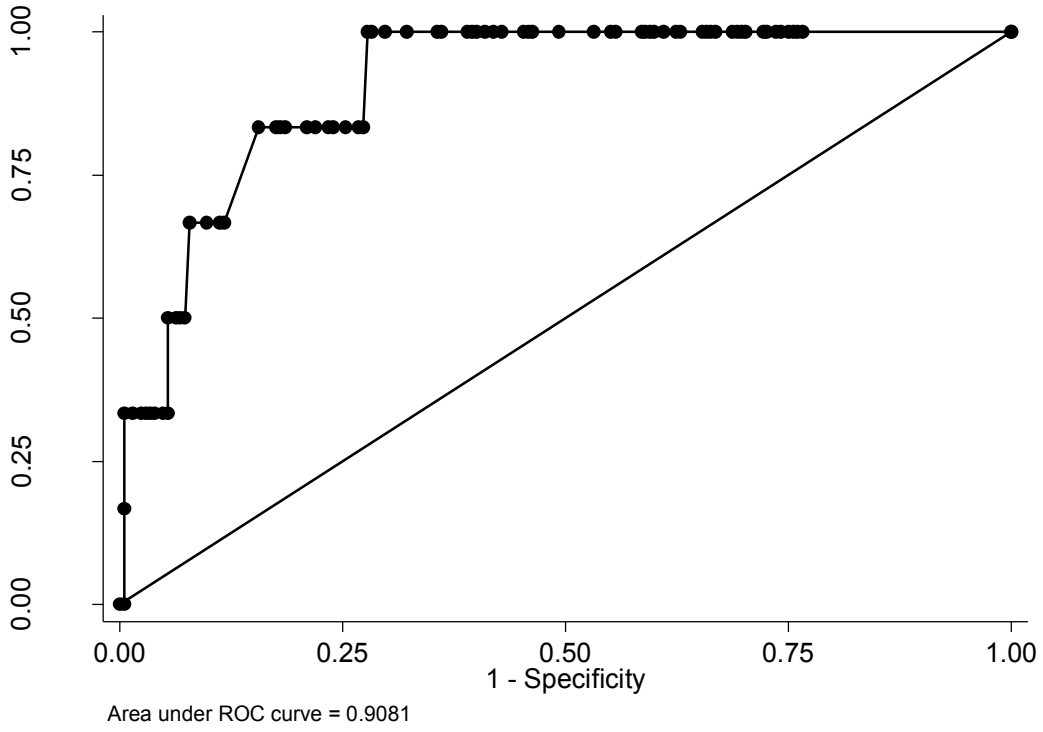
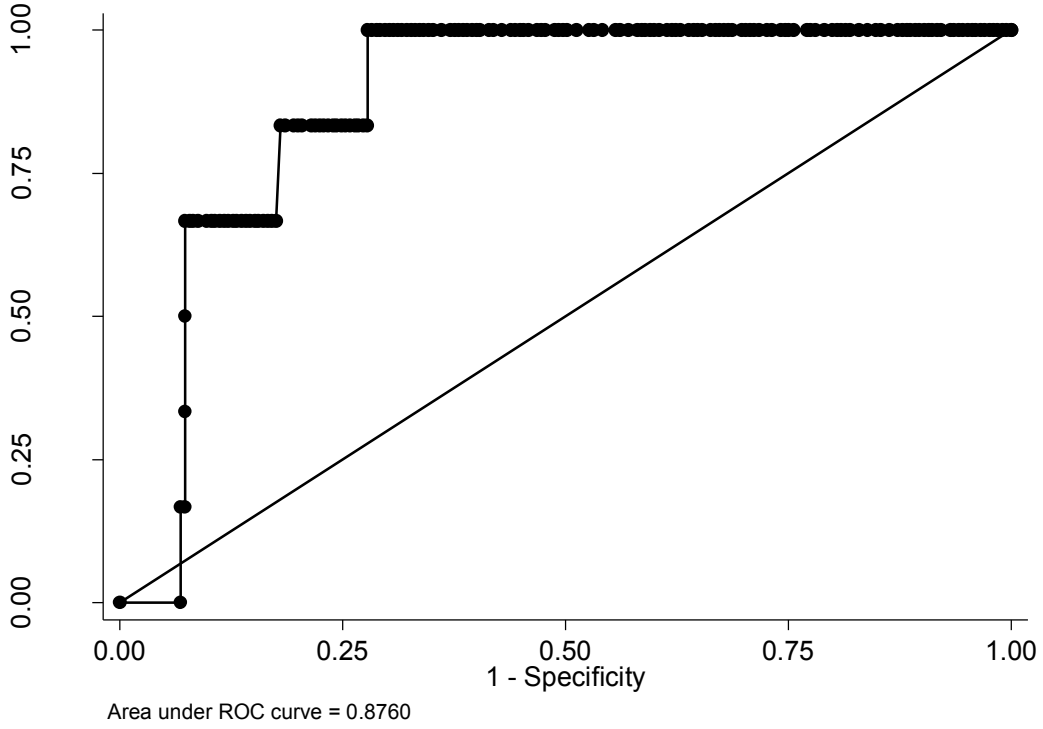


Figure 8. Receiver operating characteristic plot of cup/disk vertical ratio to detect definitive glaucoma (Right eye; n=209)



13.3. The STARD (Statement for Reporting Studies of Diagnostic Accuracy) (Ann Intern Med. 2003;138:W1-W12)

A group of scientists and editors has developed the STARD statement to improve the quality of reporting in publications on diagnostic accuracy. The statement is based on a 25 item checklist that authors should use to improve reporting. We have adhered to this checklist while preparing the manuscript. However, due to space restrictions and editorial comments, some of the text was excluded from the published paper. We have included in the thesis some omitted sections as described below.

1. Identify the article as a study of diagnostic accuracy (recommended MeSH heading "Sensitivity and Specificity"). "Sensitivity" and "specificity" were included as keywords when submitting the manuscript.
2. State the research questions or study aims, such as estimating diagnostic accuracy. The objective was stated as "To estimate the diagnostic accuracy…"
3. Describe the study population: the inclusion and exclusion criteria, setting and locations where data were collected. See Methods section of manuscript under "patient population", 2nd paragraph.
4. Describe participant recruitment: was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard? See Methods section of manuscript under "patient population", 3rd paragraph.
5. Describe participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? Consecutive series as described in Methods section of manuscript under "patient population", 3rd paragraph.
6. Describe data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)? Yes, prospective study in this regard.
7. Describe the reference standard and its rationale. See chapter 7.4 page 56.
8. Describe technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard. See manuscript, methods sections: "patient population" 3rd paragraph (scan same day as clinical exam or within 1 month), "optical coherence tomography scan" and "outcome measures" for explanation regarding use of the 5th and 1st percentiles of the normative database.
9. Describe definition of and rationale for the units, cutoffs of the reference standard. See chapter 7.4 page 56 and the methods section of the manuscript under "Final diagnostic classification" on page 454 of manuscript.
10. Describe the number, training and expertise of the persons executing and reading the index tests and the reference standard.The Stratus scans were performed by ophthalmic technicians or ophthalmic photographers with 1 or more years of experience scanning eyes with the device. Two ophthalmic technicians and 1 photographer participated in this research project. The index tests do not require subjective interpretation because the Stratus printout supplied by the manufacturer classifies the measurements by comparing them to those of the normative database. The reference standard (definitive glaucoma)

was determined by 1 of 2 ophthalmologists with subspecialty fellowship training in glaucoma.
11. Describe whether or not the readers of the index tests and reference standard were blind to the results of the other test and describe any other clinical information available to the readers. At the time of the optic nerve head examination and interpretation of the visual field test, the ophthalmologist was blind as to the results of the Stratus scan.
12. Describe methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g., 95% confidence intervals). See statistical analysis section of manuscript on page 456.
13. Describe methods for calculating test reproducibility, if done. The reproducibility of the Stratus was not calculated in this study.
14. Report when study was done, including beginning and ending dates of recruitment. See methods section of manuscript in "patient population" section where it is stated that recruitment was performed between August 2003 and May 2008.
15. Report clinical and demographic characteristics of the study population. See Table 2 of manuscript.
16. Report the number of participants satisfying the criteria for inclusion that did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test. See figure 1 of manuscript, results section of manuscript and section 7.3 of thesis regarding excluded patients.
17. Report time interval from the index tests to the reference standard, and any treatment administered between them. Stratus scans were performed the same day or within 1 month of the clinical examination.
18. Report distribution of severity of disease in those with the target condition. See Table 2 of manuscript showing clinical diagnoses.
19. Report a cross tabulation of the results of the index tests by the results of the reference standard. This tabulation could be calculated from the sensitivity and specificity percentages using definitive glaucoma as a reference standard. We considered it more informative to include the tables and graphs included in the manuscript.
20. Report any adverse events from performing the index tests. None
21. Report estimates of diagnostic accuracy and measures of statistical uncertainty. See results section with 95% confidence intervals.
22. Report how indeterminate results, missing responses and outliers of the index tests were handled. See figure 1 and results section of manuscript (first 2 paragraphs).
23. Report estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done. Not done.
24. Report estimates of test reproducibility, if done. Not done.
25. Discuss the clinical applicability of the study findings. See discussion of the manuscript and section 8 of the thesis.

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