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Diagnostic Accuracy of Tele-ophthalmology for Diabetic Retinopathy Assessment: A Meta-analysis and Economic Analysis

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

DIAGNOSTIC ACCURACY OF TELE-OPHTHALMOLOGY FOR DIABETIC RETINOPATHY ASSESSMENT: A META-ANALYSIS AND ECONOMIC ANALYSIS

(Thesis format: Integrated Article)

by

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Abstract

Tele-ophthalmology is a screening alternative that facilitates compliance to eye care guidelines regardless of geographic constraints, promoting adequate delivery of health services to underserved communities. We conducted a systematic review and meta-analysis to assess the diagnostic performance of tele-ophthalmology (TO) programs for the detection of diabetic retinopathy (DR), and used decision-tree modeling to explore its cost-effectiveness compared to in-person examination in a semi-urban scenario. From the 1,060 articles initially identified, 23 met inclusion criteria for data extraction. The diagnostic performance of TO for the detection of any DR and referable DR met the minimum diagnostic criteria by the Canadian Ophthalmological Society (sensitivity >80%, specificity >90%). Interpretation of clinical significance is limited due to significant heterogeneity. Considering a semi-urban scenario, the incremental cost per additional case of any DR detected after the introduction of pharmacy-based TO was $314.1, being more costly and more effective than in-person examination.

Keywords

Tele-ophthalmology, tele-medicine, diabetic retinopathy screening, digital photography, diagnostic accuracy, meta-analysis, economic analysis, decision tree modeling.

Co-Authorship Statement

Chapter 3 *Estimating the Diagnostic Accuracy of Tele-ophthalmology for Diabetic Retinopathy Screening: A Meta-analysis*

Co-authorship Coronado AC, Singh H, Martin J, Costella J, Malvankar-Mehta MS, Xie B, Hodge WG

Hodge WG and Coronado AC framed the study concept and study design. Coronado AC, Singh H and Costella J participated in the literature search and article retrieval. Coronado AC, Singh H and Hodge WG performed the data extraction and classification. Data analysis and interpretation was conducted by Coronado AC, Martin J and Hodge WG. Coronado AC, Martin J and Hodge WG were responsible of manuscript drafting and initial revisions. Content feedback was provided by Malvankar-Mehta MS, Martin J, Xie B and Hodge WG. Coronado AC and Hodge WG had full access to all of the data.

Chapter 4 *Cost-effectiveness Analysis of Diabetic Retinopathy Screening With Pharmacy-based Tele-ophthalmology Versus In-person Eye Examination*

Co-authorship Coronado AC, Zaric GS, Martin J, Malvankar-Mehta MS, Hodge WG

Hodge WG and Coronado AC conceived the study. Coronado AC, Zaric GS and Hodge WG conceptualized the decision-tree model. Cost data and effectiveness data was collected by Coronado AC. Data analysis and interpretation was conducted by Coronado AC, Zaric GS and Hodge WG. Coronado AC, Malvankar-Mehta MS and Hodge WG were responsible of manuscript drafting and initial revisions. Content feedback was provided by Malvankar-Mehta MS, Martin J, Zaric GS and Hodge WG. Coronado AC and Hodge WG had full access to all of the data.

Dedication

I dedicate this work to my nieces Daniela, Sofia & Isabel, and to my nephew Samuel.

Believe in yourselves and pursue your dreams with discipline and perseverance.

I will always be there to support you.

I love you immensely.

- AC. (2014)

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List of Abbreviations

AAO	American Academy of Ophthalmology
ATA	American Telemedicine Association
CI	Confidence Interval
COS	Canadian Ophthalmological Society
DM	Diabetes Mellitus
DOR	Diagnostic Odds Ratio
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
HSROC	Hierarchical Summary Receiver Operator Characteristic curve
ICER	Incremental Cost Effectiveness Ratio
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NPDR	Non-proliferative diabetic retinopathy
PDR	Proliferative Diabetic Retinopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
QALY	Quality Adjusted Life Year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SVL	Severe Vision Loss
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

Chapter 1 Introduction

1 Introduction

Diabetic retinopathy (DR) is a sight-threatening condition involving the retinal microvasculature in type I and type II diabetic patients.[1] Although treatments such as laser photocoagulation and anti-VEGF therapy can mitigate the progression of DR, it remains one of the main causes of vision loss and blindness in the working age population in industrialized countries.[2,3] Screening for DR is a key component for timely treatment delivery, and it remains one of the main challenges to reduce cases of vision loss.[4,5] Diabetic patients tend to be non-compliant to eye examination guidelines, as less than 50% attend annual screening as advised by the American Academy of Ophthalmology.[6,7] Low availability of eye care professionals to assess DR, lack of awareness about the effects of diabetes on vision, and reluctance of undergo a dilated eye examination are among the main reasons for noncompliance.[8,9]

Tele-ophthalmology has emerged as a promising alternative to in-person eye examination for DR screening.[10] It uses digital photography and electronic communications to promote eye examination in non-specialized settings, where the patient and the specialist are in different geographical locations[11]. This system has the potential to facilitate eye screening delivery to diabetic patients, while transferring some of the workload of routine eye care examinations from specialists to other settings.[12]

Achieving a high diagnostic accuracy is an important factor for success in a tele-ophthalmology screening program.[13] Factors such as pharmacologic dilation, number of fields and population characteristics may influence the effectiveness of the program.[14] The first objective of the present study was to quantitatively synthesize the evidence available regarding the diagnostic accuracy of tele-ophthalmology strategies for DR screening, and shed some light about screening factors that may play a role in the correct identification of patients with DR. The second objective was to conduct a cost-effectiveness analysis of a pharmacy-based tele-ophthalmology program in type I and II diabetic adults from non-urban locations of Southern Ontario.

1.1 Structure of thesis document

In compliance with the standards outlined by Western University School of Graduate and Postdoctoral studies, this thesis is presented in the integrated-article format. A comprehensive review of the related literature is covered in Chapter 2. The work comprising the thesis objectives is presented as two manuscripts. Chapter 3, *Estimating the Diagnostic Accuracy of Tele-ophthalmology for Diabetic Retinopathy Screening: A meta-analysis,* addresses the first objective, while Chapter 4, *Cost-effectiveness Analysis of diabetic Retinopathy Screening With Pharmacy-based Tele-ophthalmology Versus In-person Examination*, explores the second objective. Lastly, Chapter 5, *Integrated Discussion*, summarizes the main findings of this thesis in its global context.

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Chapter 2 Literature review, Thesis rationale and Thesis objectives

2.1 Literature review

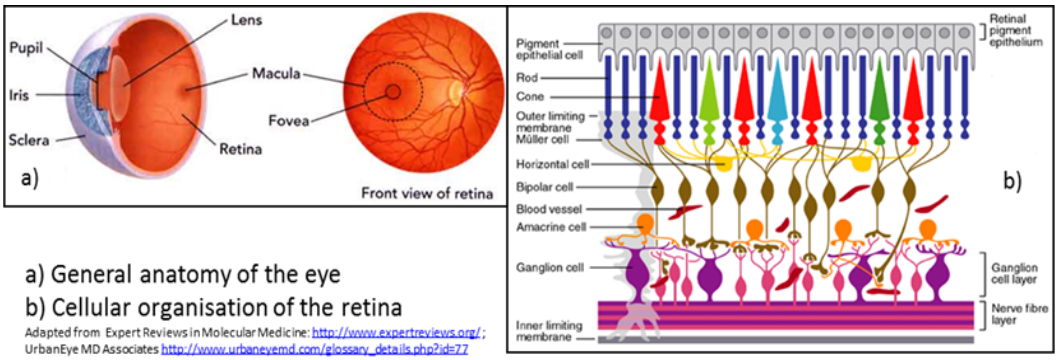
Diabetic retinopathy (DR) is a serious microvascular complication in diabetic patients, which can have a sudden and debilitating impact on visual acuity, eventually leading to blindness.[1,2] Features of diabetic retinopathy begin with micro-aneurysms and progress into exudative changes, ischemic changes, venous beading and abnormal vessel growth.[3] Improved medical care over the last three decades (intensive insulin therapy and tight blood glucose control) has reduced the progress of vision-threatening retinopathy.[4] However, it remains a challenge to prevent retinopathy and other complications before the onset of advanced stages of disease to provide a timely treatment that could lead to reducing vision loss by 50%.[5,6] To achieve this goal, it is necessary to have scheduled regular eye examinations to ensure a reliable detection at time when treatment (e.g. laser therapy, or anti-VEGF treatments) is most effective. Lack of compliance to screening guidelines, limited availability of retina specialists and ophthalmologists in several geographic areas and socioeconomic barriers are the main challenges to improve visual outcomes in diabetic patients.[7,8]

2.1.1 Natural History of diabetic retinopathy

Although fundamental causes are uncertain, exposure to elevated glucose and other risk factors initiates a cascade of biochemical and physiological changes that take place before the onset of vascular lesions in patients with clinically normal retinas.[9] Normal vision relies on the perfect cell-cell communication among epithelial cells on the retina, mainly neuronal, glial, microglial, vascular and pigmented cells (**Figure 2.1**).[4] Vascular changes in diabetic patients such as increased retinal flow and permeability of small vessels, if left uncontrolled, could lead to glucose-mediated microvascular damage in retinal structures conducting to progressive vision loss.[2]

While the interval between diabetes diagnosis and development of any retinopathy varies from 4 to 7 years (or longer), functional and anatomic changes do occur shortly after the onset of insulin-deficient diabetes, corresponding to the preclinical retinopathy stage.[10–12] During this stage, early histological changes such as pericyte loss and basement membrane thickening are the main cellular events affecting

retinal function, but are only detectable by histological examination and cannot be identified clinically. These changes affect the growth and repair of endothelial cells in the retinal vascular system; pericyte loss in particular affects normal capillary perfusion, which increases membrane permeability and causes extravasation of intravascular fluid.[9,13,14] To prevent the progression of this early phase to more severe vascular lesions, it is recommended that patients with normal-appearing retinas and good vision should already have a specific screening schedule as well as a solid preventive treatment to control for other known risk factors that could accelerate the onset of DR.[3,4] These individuals also represent an important therapeutic opportunity since they will have a better response to intensive therapy and an increased chance to preserve vision loss.[4]



a) General anatomy of the eye
b) Cellular organisation of the retina
Adapted from Expert Reviews in Molecular Medicine: http://www.expertreviews.org/; UrbanEye MD Associates http://www.urbaneyemd.com/glossary_details.php?id=77

Figure 2.1 Anatomy of the retina

As preclinical retinopathy remains undetected, the combined effect of pericyte loss and expression of angiogenic factors by nonvascular retinal cells leads to the onset of clinical manifestations of nonproliferative diabetic retinopathy (NPDR), such micro-aneurysms and intraretinal microvascular abnormalities localized within the retina (IRMA).[4,13] Other defects such as capillary dilation, nonperfusion and leakage are also developed predominantly in the posterior fundus temporal to the macula, compromising neuronal and glial cell integrity which in turn have a negative impact in neurotransmission.[4,15] As DR progresses, new retinal vessels in the optic disc are formed as a consequence of the permanent expression of VEGF factor, cytokines and other components involved in inflammatory response. When neovascularization and retinal vasodilation beading takes place, the disease has progressed to proliferative diabetic retinopathy (PDR). The cumulative effect of vascular and neural alterations

taking place in both the retina and optic nerve (e.g. macular edema, retinal detachment, optic neuropathy and axonal degeneration) along with presence of media opacities lead to vision loss.[16]

2.1.2 Epidemiology of diabetic retinopathy

Diabetic retinopathy is recognized as a public health problem among industrialized nations, as it remains the main cause of blindness in people aged 20 to 74 years of age. In north American adult type 2 diabetic patients older than 40 years, 40% have retinopathy and 8% have progressed to vision-threatening retinopathy.[17] Important risk factors include hyperglycaemia, diabetes duration and concomitant hypertension.[18] Vision-loss rates have been decreasing over the past three decades, due to the advent of photocoagulation treatment for DR patients and newer anti VEGF treatments. However, a timely identification of at-risk patients is of great importance for adequate treatment delivery.[19]

2.1.2.1 Prevalence

In many industrialized countries, DR is the most frequent cause of vision impairment in both the elderly and the working-age population[20]. A recent meta-analysis conducted by Yaw JWY and colleagues, revealed that the global age-adjusted prevalence of any DR is 34.6% (95% CI: 34.5-34.8) among diabetic patients[21]. A higher prevalence of any DR among type I DM patients was also found (77.3%), when compared to that of type II DM counterparts (35.2%). Similarly, prevalence estimates were higher in African-Americans (49.5%) and lower in Asians (19.1%); moreover, no significant gender difference in DR prevalence was found [21]. Other studies conducted in United States and Australia have reported lower prevalence[22]. In United States the estimated prevalence of any DR for diabetic individuals over 40 years is 28.5%, whereas in Australia is 21.9% for individuals over 25 years with type II diabetes[23,24]. Of important note, rural communities seem to have particularly high DR prevalence. A study conducted in rural China named The Handan Eye Study, showed a prevalence of any DR of 40% in diabetic patients over 30 years of age[25].

Recent studies conducted in Canada have taken place in Alberta, James Bay and the Metis Nation, revealing conflicting prevalence estimates. Studies such as The Southern Alberta Study for Diabetic Retinopathy (SASDR)[26] conducted in both urban and rural areas revealed a prevalence of any DR of 40%, almost two-fold greater than the one reported by Nathoo and colleagues (27.2%) for rural northern Alberta[27]. Similarly, a study conducted in Alberta First Nations communities by Rudnisky and colleagues using a tele-ophthalmology screening strategy, found a prevalence of any DR of 20.71%[28]. Such differences might be due to selection bias or might reflect a true difference in disease burden.

Although it has been proposed that native communities are more susceptible to develop diabetes-derived vascular complications such as DR[29,30], the SASDR study did not find differences in prevalence of any DR between native and non-native Canadians[26].

2.1.2.2 Incidence

Very few population-based studies have reported the incidence of DR; the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is perhaps the most widely known[31]. This study conducted in the United States, included type I and II DM patients from 11 counties in south central Wisconsin with the main objective of providing a stable estimate of risk of DR according to age group (less than 30 years and equal or older than 30 years)[32]. The results showed that, in a 10-year interval the overall incidence of DR was 74%; 17% of patients diagnosed with DR at baseline developed PDR during that same timeframe[33]. After 25 years of follow-up (1980-1982 to 2005-2007), almost all patients with type I diabetes developed DR (97%) from which 42% progressed to PDR[34].

A recent study conducted in England by Jones and colleagues, included type I and II diabetic patients screened by the Central Norfolk Diabetic Retinopathy Screening Service between 1990 and 2006[35]. At baseline, 20.5% of patients had at least pre-proliferative retinopathy. Overall incidence rates of any DR after 5 and 10 years of follow-up were 41.3% and 84.7%, respectively. Likewise, after 10 years of follow-up 11% of patients with pre-proliferative retinopathy at baseline developed PDR. Unlike

the WESDR study results, the incidence rate of PDR was lower, probably due to a selective exclusion of high-risk patients that were referred to a specialist, and thus removed from the screening cohort[35].

While the trend of DR incidence for type I and II diabetic patients is not well established, there is evidence that progression to PDR has been decreasing throughout time[6]. A systematic review conducted by Wong and collaborators, included 28 studies from 1975 to 2008 to determine temporal trends and rates of progression of DR to PDR[36]. Among studies that reported the incidence rate after 4 years of follow-up, the pooled incidence of PDR was 11%. After stratifying by time points, it was found that 19.5% of patients developed PDR in 1975-1985 in contrast to just 2.6% in the 1986-2008 cohort[36]. Such difference might be partially explained by the improvement in DR screening methods and treatment guidelines for diabetic patients, as well as a better glycemic control in recent years[37].

2.1.2.3 Risk of blindness and severe vision loss (SVL)

Vision loss is the most important functional consequence of DR. Despite the availability of novel treatments to prevent severe vision impairment from DR, it is clear that blindness from diabetes remains a public health concern in most countries[31,38]. A meta-analysis conducted by Wong and associates, found a rate of severe vision loss (visual acuity <5/200) of 2.6% in studies published between 1986 and 2008[36]. Moreover, SVL was more likely to develop in patients with untreated DR at baseline, which highlights the importance of an early diagnosis and a timely intervention[36,39,40]. .

Also important is the burden of legal blindness (<20/200) and visual disability (<20/70) due to advanced forms of DR. In the WESDR study for example, 3.6% of insulin requiring participants were legally blind (visual acuity <20/200 in the better eye) at the baseline examination[34,41]. Even mild forms of visual impairment have a considerable impact on quality of life, as patients with impaired visual acuity report low socialization,[42] emotional distress and difficulties in physical function related to driving and distance vision.[43] As a result, these debilitating ramifications of loss in visual acuity may lead to a significant reduction in the functional status of the

patient, taking a toll to society.[9] Thus, prompt classification of DR and appropriate treatment according to DR severity becomes crucial to reduce its progression and to subside the impact on visual acuity.

Evidence of decreasing vision loss rates has been reported in recent studies [44]. Klein *et al*, reported a decrease in vision loss incidence rates in more recently diagnosed type I diabetic patients (annual incidence rate 1.19% in early 1980's vs. 0.30% in mid-2000's), which might be due to a combined effect of better glucose controls, timely treatment interventions and a lower incidence of PDR[45].

2.1.2.4 Risk factors

2.1.2.4.1 Modifiable factors

- *Hyperglycemia*

Glycemic control is currently considered an important predictive factor for DR, although its influence in onset and progression of DR wasn't established until early 1980's.[31,40] Epidemiological findings from large population studies such as WESDR,[41] the Diabetes Control and Complications Trial (DCCT),[46] and the UK Prospective Diabetes Study (UKPDS)[47] helped to determine whether the level of hyperglycemia influences the risk of retinopathy. Specifically, evidence from the WESDR study showed that for every 1% decrease in glycosylated hemoglobin A1 level (HbA_{1c}) there was an association with an 18% decrease in the 21-year progression to PDR in insulin requiring subjects.[34] This study also provided evidence that glycemic control was a significant predictor of 10-year rate of PDR, in both type I and II diabetic patients.[48]

Findings from the WESDR study were further confirmed by subsequent outcomes from the DCCT (Type I DM patients) and the UKPDS (Type II DM patients) trials. In the DCCT trial, it was proven that intensive glycemic control (median HbA_{1c}, 7.2%) led to a reduction of 76% (95% CI:62-85) in the development of DR among insulin-requiring patients without DR at baseline.[46] Similarly, patients in the intensive glycemic treatment group had a lower progression rate from early to advance DR by 54% (95%CI: 39%-66%), as compared to patients in the conventional treatment group. This means that subjects with HbA_{1c} levels of 10% have a 5-fold increase risk

of DR progression, as compared to patients with 7% HbA_{1c} levels.[46,49,50] In line with these findings, the UKPDS reported equivalent findings for type II diabetic patients.[47] After 10 years of follow-up, patients in the treatment-intensive group (dietary restriction plus medication) had a 25% (95%CI: 7%-40%) risk reduction of microvascular events (including progression of DR), when compared with the conventional treatment group (diet only).[51,52] Levels of HbA_{1c} were also lower in treatment intensive patients (7% vs. 7.9%) than in their counterparts.[52]

Altogether, these studies provided evidence that intensive glycemic control is a determinant factor for reducing the risk of development and progression of DR in both type I and II diabetic patients. In fact, they founded the basis for the American Diabetes Association guidelines for glycemic control to reach a target level of HbA_{1c} of 7% for diabetic patients.[40]

- *Hypertension*

It is hypothesized that hypertension might contribute to an increase of retinal blood flow, which in turn promotes the onset of DR.[53] Some epidemiologic studies have found evidence of an association between hypertension and DR progression, although its influence in DR onset is not well established yet, especially in type I diabetic subjects.[5,20] In the WESDR study, blood pressure was related to the progression of PDR in insulin-dependent patients (HR, 1.3 per 10 mmHg; 95% CI: 1.16-1.46; p-value < 0.001), but hypertension at baseline was not associated with incidence of DR (HR, 1.1; 95%CI: 0.86-1.44; p-value, 0.42) in type I diabetic patients.[34] In contrast, the UKPDS study randomized eligible type II diabetic patients with borderline or mild hypertension to receive tight blood pressure control (<150/<85 mmHg), or conventional control (<180/<105 mmHg).[47] Patients having a tight control had a 34% reduction (99%CI: 11%-50%) in the progression of DR, and a 35% reduction in laser photocoagulation compared with patients in the conventional control group[52,54].

- *Other risk factors*

Results from some epidemiological studies have found that other modifiable factors such as dyslipidemia, obesity and inflammatory markers are somewhat associated with DR[20,37]. However, findings have been inconsistent and their particular role in the

pathogenesis of DR has not been yet elucidated. Although studies have failed to demonstrate an association of DR progression and total cholesterol levels, data from two large cohort studies[55,56] have found that high serum lipids at baseline are related to the development of hard retinal exudates. Specifically, increasing triglycerides and lower HDL cholesterol were reported to be potential risk factors for the progression of DR in type I diabetic patients[57,58]. Such findings were also confirmed by a cross-sectional analysis of insulin-requiring European patients, in which subjects with elevated triglyceride levels presented a doubled risk of DR progression, when compared to patients in the lowest triglyceride quartile[59].

The relationship between body mass index (BMI) or waist to hip ratio and DR progression is still inconclusive. Some studies have found that higher BMI and neck circumference are independently associated with the presence and severity of DR[60,61]. In contrast, large scale studies such as WESDR have suggested a protective role of BMI in DR progression among type I patients. It is evident that more research is needed to clarify the role of obesity in DR onset and progression[62]. Similarly, evidence regarding the role of inflammatory markers as risk factors for DR is at an early stage, in which markers of inflammation such as C-reactive protein, interleukin-6 and soluble intercellular adhesion molecule 1 have been associated with retinopathy and proposed as novel therapeutic targets as well[60,63]. Compelling epidemiologic evidence is necessary to understand the role of markers of inflammation in DR pathogenesis and the possibilities of clinical use as therapeutic targets for retinopathy prevention.

2.1.2.4.2 Non-modifiable factors

- *Duration of diabetes*

The role of diabetes duration in the development of DR is well established, and has been consistently demonstrated in several studies.[5,6,20,64,65] For instance, two population studies conducted in the United States reported increased DR among patients with ≥ 15 years of diabetes. The Los Angeles Latino Eye Study (LALES) reported a four-fold increased incidence of DR in the first eye for patients with more than 15 years of diabetes as compared to individuals with newly diagnosed

individuals (p=0.004).[64] In line with these findings, Harris and collaborators showed a higher prevalence of DR in type II diabetic patients with 15 or more years since diagnosis versus subjects with less than 5 years of diabetes (36% and 11.8% respectively, p <0.001).[66]

- *Ethnicity*

Research studies have demonstrated some disparity in the prevalence and severity of DR among ethnic groups, which sometimes has been independent from other known risk factors.[6,67] Some studies conducted in the United States have reported that members from Hispanic and African American communities have a greater risk of DR when compared to non-Hispanic white counterparts.[64,66,68] For example, the Multi-ethnic study of Artherosclerosis (MESA) reported a higher DR prevalence (p= 0.01) among black and Hispanic people (36.7% and 37.4%, respectively) than in white subjects (24.8%). Although ethnic origin was not an independent predictor of DR, researchers have speculated that genetic factors might explain the excess risk of DR in some ethnic groups.[17,49,51,52] In a subsequent analysis, the DCCT study investigators assessed familial associations and risk of DR in more than 300 participants[69]. It showed an increased risk of severity of retinopathy among relatives of retinopathy-positive patients when compared to relatives of retinopathy-negative subjects (OR= 3.1; p < 0.05).[69]

Altogether, such evidence suggests that differential genetic predisposition to microvascular damage, or even intrinsic cultural factors among ethnic groups might have an underlying role in the development of DR. However, greater exposure to hyperglycemia and higher frequency of risk factors (i.e. poor glycemic control) in African Americans and Hispanic individuals versus white subjects might also account for reported differences in DR development among ethnic groups[66].

- *Other non-modifiable risk factors*

It is speculated that hormone elevation levels occurring after puberty are positively associated with retinopathy[70]. Studies conducted in the past two decades reported that prepubertal duration of diabetes is related to increasing the delay in the onset of microvascular complications, such as DR in insulin-requiring patients.[71–73] A

subsequent analysis derived from the WESDR study, reported that diabetes duration after menarche was associated with an increased risk of retinopathy compared with diabetes duration prior menarche (OR=3.15; p< 0.05).[71] Similarly, pregnancy has been associated with an increased development and progression of DR, especially in type I diabetic patients.[74,75] In a longitudinal analysis derived from the DCCT study, pregnant women (type I diabetes) had 1.6 to 2.4-fold increased risk of retinopathy compared to non-pregnant counterparts, being the highest risk at the second semester.[76] Notwithstanding, DR developed during pregnancy shows a 30% to 50% rate of spontaneous regression after delivery with no long-term consequences.[77]

2.1.3 Clinical assessment of diabetic retinopathy

2.1.3.1 Screening techniques

A comprehensive screening evaluation for DR should include intraocular pressure and visual acuity estimations, as well as retina examinations for the presence of neovascularization.[78] The main potential screening modalities for DR assessment are ophthalmoscopy (direct and indirect), fluorescein angiography, slit-lamp biomicroscopy and mydriatic or non-mydriatic camera-based screening.[79] According to the Canadian Ophthalmology Society evidence-based guidelines, screening alternatives for DR grading should accomplish a sensitivity of at least 80% and specificity between 90% and 95%, if performed by a trained examiner.[78] Likewise, a widely used clinical standard proposed by the British Diabetic Association Working Group in 1997 specifies that methods of screening for DR should match the 80% and 95% specificity standards, keeping in mind that lower effectiveness values imply potential costs for the healthcare system and missed treatment opportunities.[80] From the mentioned alternatives, ophthalmoscopy and slit-lamp biomicroscopy are traditionally used for community-based screening. However, ophthalmoscopy shows a significant variation on the effectiveness depending on the healthcare professional that conducts the examination.[81] For example, studies that evaluated the effectiveness of screenings by optometrists and general practitioners showed that sensitivity levels for detecting sight-threatening retinopathy ranged between 25% and 80%, being optometrists more effective than general practitioners.[82–84] Similarly, studies using undilated ophthalmoscopy screening conducted by

nonophthalmologists reported poor performance, with a sensitivity as low as 50% for the detection of PDR.[81] Alternatively, the best screening approach for grading DR is dilated slit-lamp biomicroscopy, assessed by a retina specialist or senior ophthalmologist with a 90D or 78D lens. This technique has proven to be highly effective, achieving sensitivity and specificity values of 87% and 94%, respectively.[83,85]

2.1.3.2 Screening and prevention of DR

DR fulfills the World Health Organization (WHO) criteria for screening;[86] these criteria revolve around three critical components: Disease, screening test, diagnosis and treatment.

Disease

DR is an important public health concern,[87] with a recognizable presymptomatic stage and a natural history well described in the literature.[2] It is widely accepted that DR presents a long preclinical phase that may last up to 7 years, during which the patient cannot detect any vision changes.[10-12] Usually, the patient seeks medical care after severe retinal damage has occurred, for which treatment may not be effective.[9] Therefore, the detection of early stages of DR through screening facilitate adequate treatment delivery, which is translated to cases of blindness prevented. For example, some districts in Great Britain with long-standing DR screening programs have reported that DR is no longer the main cause of blindness amongst working-age individuals, as opposed to other settings that do not have a consistent screening program in place.[7]

Screening test

Several screening methods can be used for DR examination. Screening typically includes direct/indirect ophthalmoscopy, slit-lamp biomicroscopy or digital fundus photography. Their performance may vary depending on use of pharmacologic dilation, the grade of expertise of the examiner and threshold positivity. For the detection of sight-threatening retinopathy, mydriatic digital fundus photography results interpreted by an expert reader yield a sensitivity and specificity of over

80%.[82] These screening techniques are not invasive and do not cause the patient any harm; however, pharmacologic mydriasis may cause temporary blurred vision and increase the risk of temporary open-angle glaucoma.[39] Nevertheless, the benefits of early detection of DR cases outweight the potential (and reversible) harm of open-anle glaucoma.[9]

Diagnosis and treatment

Several landmark clinical trials[32,88,89] have shown the clinical benefits of timely and accurate screening that facilitates treatment delivery and prevents blindeness due to DR. For example, the Diabetic Retinopathy Study (DRS) demonstrated that panretinal photocoagulation reduces the risk of vision loss by 50% and 16% in patients with macular edema and PDR, respectively.[90] Such findings were later confirmed by the ETDRS study in older-onset diabetic patients.[91] Even novel therapies, such as anti-VEGF treatments have shown improvement in visual acuity in patients with diabetic macular edema, a serious complication derived from the progression of DR.[92] More recent studies on anti-VEGF treatments have shown that not only patients under this therapy have a long-lasting improvement in visual acuity, but also have significant regression of retinal neovascularization and reduced retinal thickness.[93] Therefore, an early intervention for DR treatment does translate in clinical improvement by preventing cases of blindness and severe vision loss in patients with moderate PDR.[90] In fact, evidence-based models have shown that with proper screening and treatment, 6% of patients would be prevented from blindness within a year and up to 34% within 10 years..

Finally, DR screening programs have proven to be cost-effective in economic modelling studies, resulting in substantial budget savings for the healthcare provider.[94,95]

Screening goals and challenges

The main goal of a screening program for DR is the detection of sight-threatening disease, in which the detection of any retinopathy is of secondary benefit but may act as an early proxy of the former.[96] Examination guidelines have been developed

by organizations such as the American Academy of Ophthalmology (AAO)[97] and the American Diabetes Association (ADA)[19] which have been largely based on retinopathy severity. According to ADA's latest guidelines, an immediate eye examination is recommended for newly diagnosed type II diabetic patients, whereas type I patients can have their first examination within 3 to 5 years of diagnosis. Annual or biannual eye examination is recommended in absence of complications, with more frequent examinations in case of abnormal findings.[19] Likewise, the AAO formulates the same differential recommendation for type I and II diabetic patients, with an annual follow-up examination for both groups.[97]

Adherence to examination recommendations has been less than satisfactory, with a 30%-60% compliance rate that varies across different settings[98]. For instance, adherence rates to vision guidelines in North America were less than 50% during the past two decades;[8] unfortunately, reported rates do not yet show an increasing adherence trend over time.[99] Studies also show that translation of research into practice and adoption of examination guidelines have been delayed by compliance barriers, in areas such as community education and finance.[100] Among these studies, the Diabetic Retinopathy Awareness Program (DRAP) trial[101] conducted in the US, reported a nonadherence rate to AAO and ADA guidelines of 30% (n= 813/2308). It also suggested four main factors associated to poor compliance: healthcare provider, population demographics, diabetes type and duration and education.[101] Low screening rates translates into negative implications for the quality of life of diabetic patients, representing potential expenditures to their clinical care, lost productivity and lost opportunities for vision loss prevention.[8]

Overall, this evidence supports the need to improve vision care practices in diabetic patients, with greater emphasis on target groups at high-risk of nonadherence.[100,101] These groups are typically from rural or remote areas and have a low level of awareness about vision complications of diabetes; improved access to healthcare (practice/provider performance) and more detailed information about DR complications would increase screening attendance.[102,103]

2.1.3.3 Grading of diabetic retinopathy severity

Currently, there are many validated DR grading scales that are applied widely in clinical and research settings, which are based on the identification of key microvascular abnormalities from each DR stage (**Figure 2.2**).[12,104,105] Among available guidelines, the Airlie House classification is universally accepted in research settings and publications, for it has demonstrated a satisfactory reproducibility and validity.[88] It is based on seven standard 30-degree photographic fields, yielding an accurate representation of the retinal status; an extensive standard set of more than 11 DR definitions is employed to classify DR severity in patients.[88] In spite of its use in clinical trials as the "gold standard" for DR screening, the implementation of the Modified Airlie House classification in the clinical setting and mass screening is somewhat unpractical due to its complexity and meticulous definitions, which are unnecessary and difficult to remember in clinical care.[104,106] In fact, the American Academy of Ophthalmology has found that most health professionals do not use the full Airlie House classification scale due to its complexity.[12]

Consequently, several countries have adapted and simplified this classification for general practice, resulting in a variety of validated guidelines, such as European field guide, Winsconsin guidelines and EURODIAB protocol, which have been used in different settings over the past decade (**Figure 2.2**).[12,104,105] It is also common to find published studies in which authors modify an existent grading guideline, or even develop their own classification to grade severity of DR in their study patients.[107,108]

The lack of consensus regarding DR severity classification poses a challenge in healthcare delivery and research, limiting the worldwide exchange of information and data.[109,110] For example, the comparison of screening strategies from different settings would be inappropriate if each study used their own grading system. It also affects the effective communication between and among primary care physicians, nurses, ophthalmologists and other eye care providers, which would be improved if a standard set of definitions of severity of diabetic retinopathy is universally implemented.[12,106,111]

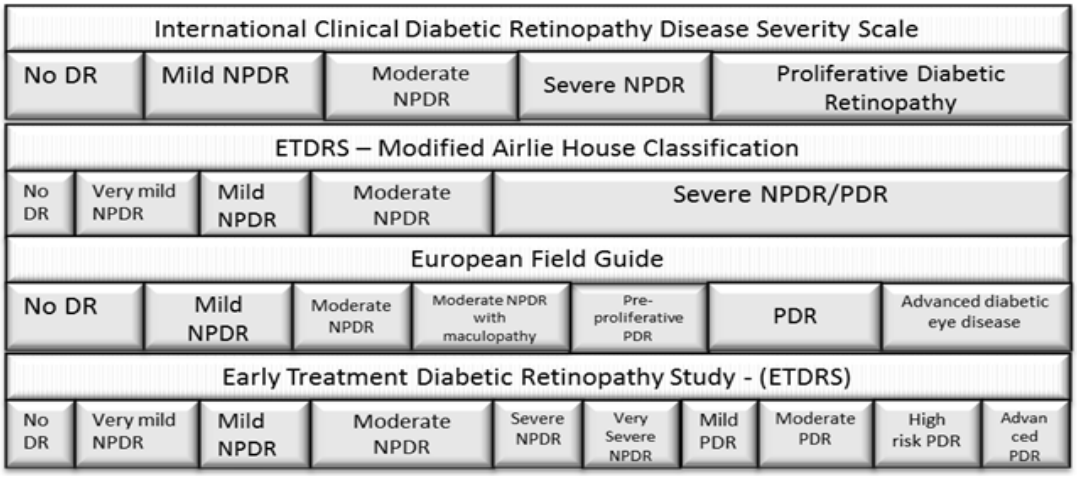


Figure 2.2 Diabetic Retinopathy Disease Severity Scales. ETDRS= Early Treatment Diabetic Retinopathy Study DR= Diabetic Retinopathy NPDR= Non-proliferative Diabetic Retinopathy PDR= Proliferative Diabetic Retinopathy

In an effort to providing a single standardized practical clinical DR severity scale for worldwide use, the AAO launched a project in 2001 to develop an optimal DR scale, resulting in the publication of the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales in 2003.[12] Based on landmark studies such as ETDRS[88] and WESDR[32], this scale comprises 5 different levels of DR disease severity according to findings of IRMA and venous beading lesions (**Figure 2.2**). It is expected that the system will be implemented by ophthalmologists and other healthcare providers, who can also promote its dissemination and future incorporation of the International DR Scale in practice guidelines.[12,78,112]

2.1.3.4 Gold standard for diabetic retinopathy screening

From the existing screening alternatives, ETDRS 30-degrees 7-field stereo color 35 mm slides is considered the gold standard for detection of DR.[94] This technique was initially used in the DRS trial[113] (1976), later expanded in the ETDRS trial[88] (1991) and validated in subsequent studies. It consists of a set of 7 photographs taken in different areas of the eye, including stereoscopic photographs centered on optic disc, macula, temporal to the macula, and upper and lower poles of the disc.[88] This method allows a detailed examination of various retinal abnormalities including micro-aneurysms, soft exudates, hard exudates and retinal haemorrhages. However, this technique is labour intensive, time consuming (it takes several weeks from data

acquisition to interpretation), and requires skilled photographers and sophisticated photography equipment.[114] Consequently, it becomes impractical for community screening and is not universally used in routine clinical care.[79]

Despite these limitations, some experts consider the ETDRS photograph protocol as the only accepted gold standard test for detecting diabetic retinopathy in research,[79,114,115] although this statement is not universally recognized. Validation studies have demonstrated that slit-lamp examination by an experienced specialist is equivalent to ETDRS photographs in the detection of referable retinopathy; hence, slit-lamp biomicroscopy has been used as a reference standard as well. In a study conducted by Scanlon and colleagues[116] in which slit-lamp biomicroscopy performed by an ophthalmologist was assessed against 7-field ETDRS photographs, sensitivity and specificity values of 87.4% and 94.9%, respectively. Hence, authors concluded that slit-lamp biomicroscopy if performed by an experienced ophthalmologist is favourably compared with 7-field ETDRS photographs in the detection of referable retinopathy.[116] Other studies have also showed a high level of agreement (kappa index > 0.75) between examination and 7-field ETDRS photographs for grading severe forms of DR, with small number of disagreements of clinical significane.[117,118]

Given that a dual gold standard exists, diagnostic accuracy studies have reported the use of either ETDRS photographs or slit-lamp biomicroscopy as the gold standard test.[115] Such contrast is explained by the fact that observational studies prefer slit-lamp biomicroscopy as the reference standard to assess diagnostic accuracy of DR screening alternatives, especially if the study is performed “in the field”. These projects are often conducted in remote areas and isolated communities, where transportation of the specialized equipment required for stereo 7-field ETDRS photographs becomes impractical and unsuitable for large-scale screening.[119,120]

2.1.4 Digital retinal photography

During the past 30 years, digital photography has been introduced as an effective alternative to ophthalmoscopy and traditional camera-based screening for DR screening programs. With the advent of digital and mobile technology, it has gradually become the preferred screening option, as digital cameras have technically

improved and become less expensive.[121] In addition to the advantages of camera-based screening (having an image record, review of disease progression and quality assurance), digital images can be immediately assessed and better quality images can be retaken if necessary.[96] With digital cameras it is also possible to transmit the images electronically to specialized centers where ophthalmologists can review them and grade the presence and extent of DR.[122]

Given the advantages of digital retinal photography, a growing number of studies have assessed its performance for DR screening in diverse settings; most results have been promising, reporting a sensitivity and specificity of above 80%[123–125] with some exceptions, where effectiveness was lower than 60%.[126] Such a contrast among studies also show that the chosen technology (i.e type of camera, resolution, image compression), number of fields taken and use of pharmacologic dilation might play an important role on the effectiveness of digital retinal photography screening.[127] Usually, nonmydriatic approaches have a lower sensitivity and a higher rate of unreadable photographs than those using pharmacologic dilation. Baeza and collaborators[128] directly addressed this issue by assessing three different screening strategies with and without pharmacologic dilation, using a nonmydriatic digital camera. Compared with 7-field ETDRS photographs, strategies using mydriasis achieved a sensitivity between 82%-85% and a specificity of 98% with a 2% failure rate, whereas nonmydriatic approaches showed a sensitivity range of 67%-82% and a specificity of 99% with a 16% failure rate.[128] Of important note, the screening strategy that used only one filed and no pharmacologic dilation had the worst sensitivity (67%; 95%CI: 54%-80%).

In contrast, other studies have reported that the use of a single field does not affect screening quality as long as pharmacologic dilation is used. A study conducted in Canada[119] evaluated the effectiveness of single field digital screening in an aboriginal community at James Bay (Ontario), since this modality is very practical and easy to perform in remote areas. Authors found that this single-field approach would be impossible to conduct without pharmacologic dilation in this community, given the high failure rate (> 50%). However when pharmacologic dilation was implemented, the failure rate improve dramatically (1.5%) and effectiveness values for detecting

referable retinopathy met the Canadian Ophthalmological Society's standards (sensitivity >80%, specificity between 90% and 95%).[119]

Although there is some evidence of the importance of pharmacologic dilation and number of fields used in digital photography screening for DR,[128,129] the extent of this influence and the interaction between both components is not well defined.[81] Moreover, the role of other technical characteristics such as camera type, resolution, image compression and storage on digital photography screening is unclear. So far, current guidelines from the Canadian Society of Ophthalmology and the AAO recommend that for digital photography screening, at least two 45° fields should be taken with pharmacologic dilation if mydriatic cameras are used, and without pupil dilation for the nonmydriatic camera models.[78,79]

2.1.5 Tele-ophthalmology assessment of diabetic retinopathy (telescreening)

Tele-ophthalmology is an area of telemedicine that allows the examination of patient's eye problems with the patient and eye care specialist located in different geographical areas. This method is based on the exchange of medical information from one site to another using electronic communications.[114] It has been described as a promising alternative that improves access to screening regardless of geographic constraints; it also reduces travel time and cost while creating new screening opportunities in underserved communities.[130]

Although considered futuristic and experimental during the early 80's, tele-ophthalmology has gradually evolved into a specialty that incorporates modern technology with the potential of becoming an integral component of primary care of diabetic patients.[131] Diabetic retinopathy telehealth programs typically encompass four elements of care: Image acquisition, image review and evaluation, patient care supervision, and image (data) storage.[132]

Technical requirements may vary, depending of each screening program scope and intent.[133] In a general tele-ophthalmology program for DR screening (store-and-forward model), retinal images are obtained with digital retinal cameras (mydriatic or non-mydriatic) by a previously trained non-specialist in a remote place.[114] The data is then securely transferred to a reading center for evaluation, in which ocular

assessment is performed by an eye specialist or a certified reader; specifications regarding image compression, bandwidth, encryption and error checking mechanisms are tailored according to each screening program.[132] Finally, findings are reported back to the primary care physician with the recommendation regarding the need for referral.[134]

In some cases images may be of poor quality due to presence of media opacities, small pupil size or technical difficulties.[129] In telescreening for DR, unreadable images are considered positive findings and patients must be referred for a comprehensive evaluation.[135] To overcome this issue, the use of pharmacologic agents for pupil dilation may be incorporated in the screening protocol. However, the use of mydriatic agents by nonophthalmic personnel may represent an issue in that adverse events such as angle-closure glaucoma might occur, requiring the need of specialized personnel.[119,136]

2.1.5.1 General tele-ophthalmology guidelines

Tele-ophthalmology is a mature telehealth specialty with well-established standards defined by the American Telemedicine Association (ATA), which seeks to improve healthcare delivery through telecommunications and information technology, while eliminating barriers to the use of telemedicine.[132] According to the ATA, the main goals of a tele-ophthalmology program for DR are to "reduce the incidence of vision loss due to DR, improve access to diagnosis and management of DR, decrease the cost of identifying patients with DR".[135] As clearly stated by the American Telemedicine Association[135] and the American Academy of Ophthalmology[97], retinal telemedicine examination is currently not intended to replace a comprehensive eye examination by an experienced ophthalmologist, but to act as a first-line screening tool for DR that will filter and reduce the volume of unnecessarily referred patients.

Tele-ophthalmology systems are categorized into three groups depending on image transmission: Real-time, store-and-forward, and hybrid. Real time transmission involves a two-way real time video connection, whereas in store-and-forward teleconsultation the image is first captured with a digital camera in a fixed or mobile telescreening unit and then sent forward via electronic communications.[137] Hybrid is

the combination of the two former approaches.[138] Current ocular telehealth practice guidelines from the American Telemedicine Association are based on the store-and-forward modality.[135]

2.1.5.2 Clinical validation of tele-ophthalmology systems

Both the AAO[85] and the ATA[135] have stressed the importance of performing pilot studies for the validation of new tele-ophthalmology programs. This validation must state the scope of the program, target population, aimed validation category and technology used. Ideally, results should be published in a peer-review journal in which sensitivity, specificity and agreement values are reported.[132,139] It is considered that the current benchmark for evaluating a tele-ophthalmology program consists on the use of 7 field ETDRS photographs as the reference standard, and the use of the International DR Disease Severity Scale as the guideline for DR classification.[12,88]

To outline a standard for the validation process, the ATA recently published the second edition of "Telehealth practice recommendations for diabetic retinopathy"[135], in which four categories for validation of tele-ophthalmology programs for DR are documented (**Table 2.1**). Each one differs in hardware and software technology requirements, the level of expertise of staffing and support, and clinical outcomes. Those programs with low thresholds for referral need not follow strict DR classifications and technological requirements are simpler compared to those programs that seek to discriminate level of DR.[140] Independently of the validation category, tele-ophthalmology programs should have less than 10% rate of unreadable images.[78]

Currently, there are no tele-ophthalmology programs that meet category 4 criteria which would allow the replacement of a comprehensive in person assessment. However, mature tele-ophthalmology programs for DR screening in the US (more than 10 years old) already have a category 3 validation in which level of DR is assessed, instead of the simpler dichotomous classification of category 1 and 2 programs.[132]

Table 2.1 Validation categories for Diabetic Retinopathy telescreening programs (American Telemedicine Association)

Validation	Description[1]	Threshold[1]	Requirements[2]
Category 1	Differentiation of retinas with no or minimal NPDR. Patients with great than minimal NPDR are referred	ETDRS > 20	Non-mydriatic cameras, single 45° field
Category 2	Differentiation of retinas with no sight-threatening DR. Patients with PDR are referred for prompt assessment	ETDRS > 45	Non-mydriatic cameras, at least three 45° fields
Category 3	Identification of patients who need prompt referral and treatment. Allows direct management of diabetic eye disease	Level of DR	Mydriatic or on-mydriatic cameras, at least three 45° fields; stereopsis recommended
Category 4	Matches or exceeds ETDRS photographs diagnosis. Allows direct management of diabetic eye disease	Level of DR	Mydriatic or on-mydriatic cameras, at least three 45° fields; stereopsis recommended

ETDRS= Early Treatment Diabetic Retinopathy
1 American Telemedicine Association (2011)
2 Telehealth methods for diabetic retinopathy and glaucoma. ARVO education course. May 4, 2013

Several tele-ophthalmology programs for DR screening have been launched among different settings and target populations in Australia[141], United Kingdom[142], France and United States[143]. For example, Australian models are focused on the rural setting, where underserved communities get a screening examination 900 km away from the specialized center.[144] Alternatively, tele-ophthalmology is also being used for inmate follow-up examinations in a Texas prison, saving ground transportation times and minimizing security requirements.[145] In North America, the Joslin Vision Network (JVN) located in Boston (MA) is an example of a validated category 3 program, with the main objective of providing adequate eye care to US veterans from the US Veteran's Administration.[143] The JVN program has also been incorporated into the Phoenix Indian Medical Center, providing diabetic eye care for Native Americans living in reservations.[146]

2.1.6 Concluding remarks

There are currently 347 million diabetics worldwide, from which 33% have signs of DR. About 50% of diabetic patients seek eye examinations, whereas the remaining 50% are still at risk of blindness from DR.[6] Unfortunately, Canada is not the exception.[78] According to a recent study conducted by Boucher and collaborators, the rate of diabetic patients who are noncompliant to DR Canadian guidelines is 68% in Quebec, Manitoba, Saskatchewan, Alberta and British Columbia. Moreover, 38% of diabetic patients in the mentioned provinces have never had an eye examination.[147] Besides lack of awareness regarding diabetic eye complications,

inaccessibility and difficulty of getting an appointment for screening is another main reason for not getting a screening examination.[138]

Discrepancies in access to eye care are unlikely to subside in the future. As the incidence of diabetes increases over 50%, the growth in the number of ophthalmologists in North America is dismal (less than 2%).[148] Consequently, an increasing number of patients will require an eye care examination at least every two years but even less eye specialists would be available to fulfill the demand for eye care.[106] Public health agencies will be unable to meet DR screening guidelines relying exclusively on the traditional in-person examination.

2.2 Thesis rationale

As described previously, tele-ophthalmology is an emerging alternative for DR monitoring, and is being explored in many geographic settings and across several scenarios of in-place physician accessibility.[114] Multiple studies have evaluated the effectiveness of ongoing tele-ophthalmology programs by means of assessing diagnostic accuracy estimates such as sensitivity, specificity and kappa values. The methods and settings vary widely among studies; equipment specifications and cut-off criteria also differ according with program needs and available technology.

To date, only three reviews have attempted to systematically summarize the effectiveness of screening programs for DR monitoring.[81,127,149] The first quantitative review was published in 1996, before the advent of tele-ophthalmology for DR care.[149] Later, Hutchinson and colleagues[81] published a systematic review on effectiveness of screening tests for DR which included 20 studies from 1987 to 1999. They concluded that mydriatic retinal photography was the most effective strategy for DR screening, even when compared to direct and indirect ophthalmoscopy.[81] However, the authors did not perform a meta-analysis to estimate the diagnostic accuracy of mydriatic retinal photography. In one recent review, Bragge et al reported a meta-analysis of tests designed to detect presence or absence of DR.[127] Using a hierarchical logistic regression approach, the overall sensitivity and specificity was 82.5% (95%CI: 75.6-87.9) and 88.4% (95%CI: 84.5-91.4), respectively.[127] The study was limited only to studies that assessed the presence of

any DR, whereas studies that evaluated the presence of referable retinopathy were not quantitatively summarized. More importantly, methodological quality of included studies was not assessed in this review.

Of note, none of these reviews were tailored to synthesize the evidence of tele-ophthalmology programs; on the contrary, they assessed all DR examination strategies besides digital photography. Their scope included many screening methods such as in-person examination (ophthalmoscopy), film camera, and polaroid camera, which are not suitable for telemedicine.[135] Hence, evidence of the effectiveness of tele-ophthalmology programs for DR assessment has been accumulating with no conclusive remarks. Furthermore, the use of pharmacologic dilation and number of fields necessary to maximize the effectiveness of tele-ophthalmology screening still remains controversial.[78,120] A systematic appraisal of the literature considering the influence of mydriasis and number of fields on tele-ophthalmology programs is deemed necessary.

Equally important is the estimation of the economic impact of these programs and the potential long-term benefits that may justify such investment. Several cost-effectiveness studies have assessed the impact of screening programs for diabetic retinopathy, from which a small subset focused on the economic evaluation of tele-ophthalmology technologies.[94,145,150] A recent review of the economic evidence of diabetic retinopathy[151] included 13 cost-effectiveness studies that aimed to compare key features of a DR screening program such as opportunistic screening as opposed to systematic screening, screening frequency and incorporation of new effective (but more costly) technologies for screening delivery. In general, studies have concluded that the implementation of DR screening programs is cost-effective.[152–154] However, the clinical and economic effectiveness of tele-ophthalmology is still uncertain, depending heavily on patient compliance, the workload for each retinal unit and the scenario in which would be implemented (urban or non-urban).[151,155,156]

In Canada, well-developed tele-ophthalmology programs are operating in the provinces of British Columbia, Vancouver and Quebec.[78] With the goal of creating new eye screening opportunities and promote regular attendance among diabetic

patients, most programs have been implemented in remote settings that do not have ophthalmologists on-site.[157,158] Although not a substitute for comprehensive eye examination, tele-ophthalmology act as a filter to identify and timely refer patients in need for a specialist examination.[135]

Interestingly, no telescreening initiative has been taken to improve eye care coverage for diabetic patients in a non-urban setting. Given the significant capital investment that such an initiative would demand, an economic analysis would aid to explore whether tele-ophthalmology is the best alternative for this specific context.

2.3 Thesis objectives

This thesis encompasses two different, yet highly dependent studies. The overall aim is to determine the diagnostic accuracy of tele-ophthalmology strategies for diabetic retinopathy screening, and to explore the cost-effectiveness of a pharmacy-based tele-ophthalmology screening program for detection of diabetic retinopathy in non-urban Southern Ontario.

Objective 1 – Meta-analysis

a) To systematically identify, review and quantitatively synthesize the evidence available pertaining to the diagnostic accuracy of tele-ophthalmology strategies for DR screening in adults as compared to reference standards (7 field ETDRS photographs or slit-lamp biomicroscopy).

b) To explore screening and study design factors that may influence the diagnostic accuracy of tele-ophthalmology assessments such as pharmacologic dilation, number of fields used, choice of reference standard and risk of patient selection bias.

Hypothesis Tele-ophthalmology programs meet the minimum effectiveness requirements advised by the Canadian Ophthalmological Society (sensitivity over 80%, specificity between 90% and 95%).[78]

Objective 2 – Cost-effectiveness analysis

To explore the cost-effectiveness of a pharmacy-based tele-ophthalmology program compared to primary care consultation (ophthalmoscopy) for diabetic retinopathy screening in Southern Ontario (Chatham-Kent region).

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Chapter 3 Estimating the diagnostic accuracy of tele-ophthalmology for diabetic retinopathy screening: A meta-analysis

Co-authorship

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3.1 Introduction

Diabetic retinopathy (DR) occurs as a microvascular complication that affects the blood vessels in the retina of diabetic patients, leading to a high risk of blindness if left untreated.[1] Although treatments for DR are effective, economic, and available within the public health system, it remains the leading cause of legal and functional blindness for working-age adults in industrialized nations, representing 4.8% of cases of vision loss worldwide.[2,3] Early detection by regular screening for DR is a key factor for its timely treatment, helping to prevent blindness and other impaired visual conditions in diabetic individuals.[4] However, only 50% of patients with diabetes mellitus (DM) follow the screening recommendations by the American Diabetes Association.[5]

Within this context, tele-ophthalmology has emerged as a possible alternative that facilitates compliance to evidence-based medicine, perhaps without geographic constraints. It may improve consistency of healthcare in a cost-effective fashion.[6–8] Tele-ophthalmology screening initiatives for DR have been tested and launched in diverse settings as an attempt of providing specialized eye care to underserved communities regardless geographic limitations, while also eliminating unnecessary traveling for patients and specialists.[9,10]

Published studies have focused on the diagnostic accuracy of digital imaging screening for DR in diverse settings for its use in store-and-forward tele-ophthalmology strategies.[9,11] A literature review reported that sensitivity and specificity of telescreening for detecting DR has been consistently high, and concluded that this model appeared to be a suitable test for DR assessment.[12] Other reviews have addressed the diagnostic accuracy of diverse screening methods for DR, including digital camera, film camera, direct examination and polaroid camera assessments.[13,14] Nevertheless, evidence on diagnostic accuracy of DR screening focused on tele-ophthalmology strategies has not been critically synthesized in a systematic review or meta-analysis.

Likewise, research and validation studies have also explored the influence of tele-ophthalmology components, namely, pharmacologic dilation, number of fields,

automated grading and image compression to assess their impact on screening diagnostic accuracy.[15–17] However, there has been much discussion about the most effective method for detecting DR in the telemedicine context, since current evidence on this topic is contradictory and sometimes inconclusive.[18,19] Bringing these studies together and synthesizing their results, will promote a better understanding of their clinical usefulness and influence on the diagnostic performance of tele-ophthalmology programs.

Furthermore, the choice of gold standard for tele-ophthalmology validation studies has been a subject of debate among specialists,[20] who claim that the current recommendation (standard 7 field ETDRS photographs) is impractical in rural settings.[6,21] Given the current gaps in the literature and the need of evidence synthesis on this field, the present meta-analysis seeks the following objectives: 1) to systematically identify, review and quantitatively synthesize the evidence available pertaining to the diagnostic accuracy of tele-ophthalmology strategies for DR screening in adults as compared to reference standards, and 2) to explore screening and design factors that influence the diagnostic accuracy of tele-ophthalmology assessments, namely pharmacologic dilation, number of fields used, choice of reference standard, type of diabetes and risk of patient selection bias. Hence, we hypothesized that tele-ophthalmology programs meet the minimum effectiveness requirements advised by the Canadian Ophthalmological Society (sensitivity over 80%, specificity between 90% and 95%).[22]

3.2 Methods

We conducted and reported this meta-analysis in compliance with the Meta-analysis of Observational Studies (MOOSE) recommendations (**Appendix A**) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (**Appendix B**).

3.2.1 Literature search

A structured search was conducted among six different databases (Medline, EMBASE, CINAHL, BIOSIS, Web of Science, Cochrane Library) from January 1998 to June 2012 (last update on January 2013), without language restrictions. Free text key

words and medical subject headings were tailored to each of the electronic databases, and included four main domains: diabetic retinopathy, diagnosis, telemedicine and evaluation studies (see list of search terms for all databases in **Appendix C**). A health information specialist (JC) contributed to the development of the search strategy, in consultation with other team members including content experts. Grey literature was addressed by manually searching electronic abstracts and dissertations from The American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology (ARVO) meetings. As a complementary search, bibliographies of eligible studies and relevant systematic reviews retrieved in the literature search were manually screened.[23] All citations from each database search were exported to the reference manager program EPPI version 4.3 (EPPI Centre, Institute of Education, London, UK), for de-duplication and screening.

3.2.2 Eligibility criteria

Primary studies reporting sensitivity and specificity outcomes of a tele-ophthalmology strategy for DR diagnosis were included; we focused on those studies that explicitly reported sensitivity and specificity estimates for the detection of any retinopathy and/or referable retinopathy amongst adult patients with type 1 or type 2 diabetes. In the present review, any approach that promoted the screening of DR by store-and-forward transmission of digital images, with the patient and the ophthalmologist being in different geographical settings was considered a tele-ophthalmology strategy.[6] The exclusion criteria were: (i) studies addressing pediatric patients (< 18 years old), (ii) editorials, commentaries and opinion articles, (iii) studies conducted in under-developed, developing or non-industrialized settings (Latin America, Eastern Europe, Africa and most Asian countries), (iv) studies with a reference standard different from 7 field ETDRS photographs or slit-lamp biomicroscopy, v) studies with less than 20 fully-screened patients.

3.2.3 Article screening

The screening strategy involved a two-step process. First, titles and abstracts were reviewed to identify potentially relevant articles. Next, full-text articles from included citations were retrieved to closely assess inclusion and exclusion criteria.

Two reviewers (AC and HS) screened citations and full-text articles in an independent fashion, and Cohen's kappa coefficients were used to examine inter-rater agreement. We interpreted kappa values as follows: 0.40 to 0.59 reflect fair agreement, 0.60 to 0.74 reflect good agreement, and ≥0.75 reflect excellent agreement.[24,25] Discrepancies were reconciled by discussion and any remaining disagreements were solved through consultation with an experienced ophthalmologist (WH), who assessed study eligibility. Articles published in language other than English were initially addressed by a translator (AC for Spanish articles, WG for French articles and independent translator for German articles) who examined the title and abstract and determined the study relevance based on first level screening questions.

3.2.4 Data extraction and quality assessment

A data extraction form was created and piloted with a subset of eligible studies. Based on the experience gained in the pilot study, the final version of the data extraction form (see **appendix D**) was used to collect the following information: Number of fully-screened patients; race or ethnicity; % type II diabetes; % prevalence; duration of diabetes; visual acuity; reference standard used; grading guideline used; cut-off criteria; index technology (i.e type of camera, resolution); field positioning and number of fields; pupil dilation; stereopsis; % unreadable images; screen display resolution; image compression. The main outcomes of interest were sensitivity and specificity, and outcomes in the form of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) if available. In cases where these values were not available, we derived the numbers from the sample size, DR prevalence and reported sensitivity and specificity.[26] Data was extracted by one reviewer (AC) and relevant predictor and outcome variables (sensitivity, specificity, prevalence and 2x2 tables, if available) were confirmed independently by a second reviewer (HS). Finally, a 2x2 table was constructed based on the data extracted from the studies, defining the patient as the unit of analysis. Primary authors were contacted in cases where studies provided insufficient information to reconstruct the 2x2 tables.

About half of the articles reported multiple results comparing different tele-ophthalmology protocols (e.g. more than one estimate of diagnostic accuracy per primary study). To avoid clustering effect,[27] we used a hierarchical approach to choose one comparison per study: (1) protocols using pharmacologic dilation and two or more field images per eye (2) protocols without pharmacologic dilation with two or more field images per eye (3) protocols with pharmacologic dilation and a single field image per eye (4) protocols without pharmacologic dilation and a single field image per eye.

Quality assessment was performed using the revised QUADAS2 (Quality Assessment of Diagnostic Accuracy Studies) criteria, which was adapted specifically for this review, as suggested by current guidelines (**Appendix E**).[28] No attempt was made to assign a score to the QUADAS2 items, as this tool is not intended to generate a summary quality score.[29,30] Instead, risk of bias of each study was assessed as high, low or unclear across the four QUADAS2 domains (patient selection, administration of the index test, reference standard and patient flow).

3.2.5 Data synthesis and statistical analysis

Categories for analysis

As planned in the study protocol, we stratified the data into two categories according to cut-off criteria. Category 1 included studies that aimed to detect any diabetic retinopathy (at least one microaneurysm observed); category 2 included studies that aimed to detect referable retinopathy (defined differently across studies). Accuracy estimated at multiple test cut-offs was available in many studies; in these cases, studies contributed one set of data points per category.

Meta-analysis

A meta-analysis was conducted separately for each category using a hierarchical bivariate random effects model, proposed by Reitsma *et al*.[31] Instead of using the diagnostic odds ratio, the bivariate approach uses sensitivity and specificity pairs as the starting point of the analysis, preserving the two-dimensional nature of the data.[32] Besides accounting for heterogeneity beyond chance, the bivariate model has

the advantage of incorporating the negative correlation that may exist between sensitivity and specificity, while accounting for variation within and between studies.[33,34] Summary sensitivity, specificity, positive/negative likelihood ratios (LR+;LR -) and diagnostic odds ratio (DOR) were calculated for each category using the bivariate method. Likelihood ratios are considered a useful measure for clinicians. The LR- indicates how likely a negative test result is in a diseased person compared to non-diseased person; conversely, LR+ estimates the frequency of a test positive result in diseased compared to non-diseased individuals.[35] The DOR is calculated by LR+/LR- and it is interpreted as the odds of positivity in diseased versus the odds of positivity in non-diseased. Values in DOR range from zero to infinity, higher values indicate better discriminatory test performance.[36]

To graphically present the results, we plotted the hierarchical SROC (summary receiver operating characteristic) graph for each category, which allows the visualization of the test performance along different thresholds.[37,38] This model developed by Rutter and Gatsonis[37] also accounts for variation within and between studies, due to its hierarchical approach.[39] Based on this model, we plotted the individual and summary sensitivity and specificity pairs in an ROC graph where the *y* axis indicates the index test's sensitivity and the *x* axis equals 1-specificity. For category 1 studies, we calculated the AUC (area under the curve) with the corresponding 95% confidence region and 95% prediction region.[40,41] If the AUC is 100% then the test discriminates perfectly between diseased and non-diseased patients, whereas an AUC of 50% indicates poor diagnostic accuracy.[42,43] Given that category 2 studies use various thresholds of test positivity, the AUC was not calculated.[40]

Heterogeneity

Initially, heterogeneity between studies was visually assessed through paired forest plots. Cochran Q (X^2 test) and I^2 statistics were used to describe study dispersion based on sensitivity and specificity estimates of included studies.[44,45] Statistical significance of Cochran Q test was assumed at a P value less than 0.10, due to the power limitations of the test. I^2 values of 25% 50% and 75% were considered of low,

moderate and high inconsistency, respectively.[44] Hierarchical ROC curve was also used to assess heterogeneity likely due to threshold effect. With the hierarchical SROC plot we were able to assess the proportion of heterogeneity likely due to threshold effect. A shoulder-like curve where studies are tangent to the ROC curve indicates that the observed variability between studies may be due to a threshold effect.[46,47]

Finally, potential sources of heterogeneity were explored using subgroup analysis.[48] We defined *a priori* the following characteristics as potential relevant covariates: Pharmacologic dilation ("yes/mixed" or "no"), number of fields captured per eye ("single" or "multiple fields"), reference standard used ("7 field ETDRS photographs" or "slit-lamp biomicroscopy"), type of diabetes ("type 1" or "type 2" diabetes) and risk of patient selection bias according to QUADAS2 criteria ("uncertain/high risk" or "low risk").[49] Due to the exploratory nature of covariate analysis and to the small number of studies per covariate, a meta-regression was not undertaken for the above mentioned covariates.[50]

As a way to evaluate the possible association of up-to-date technologies on the diagnostic performance of tele-ophthalmology programs, we executed a random effects meta-regression of the DOR as the outcome and year of publication as the independent variable.[51] Thus, we considered the year of publication as an indicator of improvement in both digital photography technologies and learning experience associated with tele-ophthalmology. We performed a t-test to assess the null hypothesis of no effect of year of publication (i.e recent technologies) on the DOR.[52] A P value <0.05 was considered statistically significant.

Sensitivity analysis and publication bias

We repeated the analysis including only studies that fully met QUADAS2 criteria in all four domains (patient selection, administration of index test, reference standard and patient flow). As a concern for publication bias, we performed a funnel plot based on DOR of each study (in logarithm scale) and their respective standard error. Finally, we tested for symmetry and small-study effect using a linear regression approach as

described by Egger *et al*.[53–55] A P value less than 0.05 was considered statistically significant for small study effect.[56] This test was also used to numerically estimate funnel plot asymmetry.

Statistical analysis was performed with Stata 12 (Stata Corp, Austin, TX USA). This study was supported by a grant from the Ontario Innovation Fund. The founding source had no role in the collection, analysis or interpretation of the data. Authors have no industry funding source or industry conflict of interest to disclose.

3.3 Results

3.3.1 Search results and study characteristics

After removing duplicates, 1060 citations were initially screened from which 156 were shortlisted for full text assessment. A total of 22 articles met our criteria for review;[7,57–78] primary authors from two included studies[74,77] were contacted for further information from whom only one replied.[74] Thus, one article was excluded due to lack of sufficient information.[77] Finally, one additional study was identified through manual search of bibliographies of selected studies, for a total of 23 included studies for data collection and analysis. Inter-reviewer agreement for study inclusion was excellent (Cohen's k=0.83). The study identification and selection process is described in **Figure 3.1**.

Characteristics of included studies are outlined in **Table 3.1**. The 23 studies included a total of 5,541 fully screened patients, with a median study size of 149 (IQR 112). Patients were mainly male (mean 54.2%), type II diabetic patients (mean 79%) of median age 57 years (IQR 10.4 years). The median prevalence of any diabetic retinopathy and referable retinopathy was 34.85% (IQR 15.2%), and 31% (IQR 41%) respectively. The majority of tele-ophthalmologic protocols used a non-mydriatic digital camera (69.6%), captured multiple field images per eye (52%) and used pharmacologic mydriasis for pupil dilation (52%). Interestingly, only 44% of studies used the recommended gold standard by the American Telehealth Association[6] (7 field ETDRS photographs), whereas the remaining 56% used slit-lamp biomicroscopy as the reference standard. Some studies evaluated the effectiveness of the tele-ophthalmology program at different thresholds, with and without pharmacologic

dilation, and used different number of fields captured per eye, thus reporting multiple diagnostic accuracy endpoints. The 23 final articles contributed to 31 sensitivity and specificity pairs in all.

3.3.2 Quality assessment

Studies varied in quality (**Table 3.2, Figure 3.2**). There were nine studies of low risk of bias across all four domains of QUADAS2 criteria. Concerns about index technology application were uniformly low for all studies in the quality assessment; similarly, all studies adequately reported blinding of image readers. The two main issues arising were related to the selection of patients and the analysis and/or interpretation criteria of the index test. Patient selection was a concern in three studies,[70,73,78] where patients were not enrolled on a consecutive or random basis. In addition, three studies[7,74,76] did not provide sufficient information to assess risk of patient selection bias. Eight studies removed from the diagnostic accuracy analysis those patients with uninterpretable results (ie. unreadable images), which may lead to overoptimistic diagnostic accuracy outcomes.[49] Similarly, some studies did not report details about the data analysis, or whether they included or not the full spectrum of patients.

Of note, less than 40% of included studies provided sufficient data about patient race/ethnicity, visual acuity measures and image compression. Moreover, only 56% of studies specified the type of diabetes. Thus, information regarding these covariates was not summarized nor incorporated in the meta-analysis.

3.3.3 Meta-analysis

A wide range of results was observed among studies detecting any DR (category 1) and referable DR (category 2). **Figures 3.3** and **3.4** show individual accuracy measures in a paired forest plot for each category. As anticipated in meta-analyses of diagnostic accuracy studies,[79] pooled results showed considerable heterogeneity between included studies, which was statistically significant among both categories (X^2 P value <0.001). Inconsistency ranged from moderate to high, except for sensitivity among studies detecting referable DR, where inconsistency was only moderate (I^2 71%; 95% CI: 57-86). The meta-analysis summary estimates were

obtained using the hierarchical bivariate approach, which is the recommended method for synthesis of diagnostic accuracy studies in presence of significant heterogeneity.[80] However, summary estimates should still be cautiously interpreted given the marked heterogeneity amongst studies.

Synthesis of results by category

Summary statistics (sensitivity, specificity, DOR, LR(+), LR(-)) and their corresponding 95% confidence intervals for both categories are outlined in **Table 3.3**.

Category 1. Detection of any DR

This category included all studies that aimed to detect any DR (at least one micro-aneurysm or worse), which involved 16 studies for a total 3,167 fully screened patients. After pooling the sensitivity and specificity of single studies using the bivariate method, we obtained a combined sensitivity of 0.89 (95% CI: 0.81-0.93) and combined specificity of 0.94 (95% CI: 0.89-0.96). As expected from pooling studies with identical cut-off criteria, the proportion of heterogeneity likely due to threshold effect was zero.

The accuracy of tele-ophthalmology for detecting any DR is graphically shown using the hierarchical ROC curve that illustrates the summary point and the individual study datapoints (**Figure 3.5a**). Using this approach, we found an AUC of 0.97 (95% CI: 0.95-0.98) and a DOR of 113 (95% CI: 51-248). Although 60% of studies are located towards the upper left of the graph indicating good test performance, the presence of outliers influences the 95% prediction ellipse downwards.

Category 2. Detection of referable retinopathy

In this category, all studies that aimed to detect "referable DR" were included. Thus we identified 15 studies, including 3,794 fully screened patients. The overall sensitivity and specificity was 0.91 (95% CI: 0.87-0.94) and 0.92 (95% CI: 0.88-0.95), respectively. According to the hierarchical bivariate model analysis, the proportion of heterogeneity likely due to threshold effect was 0.13. However, this category incorporates different thresholds which challenge the interpretation of a single

paired estimate provided by the bivariate method, as it indicates the performance of an unknown average threshold. Moreover, the prevalence of referable DR was widely spread among studies (prevalence range: 5% -77%; IQR 41%). Thus, it is more adequate to base the analysis on the hierarchical SROC plot that allows assessing the performance of the test taking all thresholds into account, and visualize individual study results (**Figure 3.5b**).[81] The distribution of the studies in the plot shows a greater variability in specificity rather than sensitivity.

Subgroup analysis

Results from subgroup analysis are presented in **Table 3.4**. Due to the limited number of studies available in category 1 (detection of any DR), covariance analysis of studies that used a single field per eye was not possible. Otherwise, all remaining *a priori* subgroup analyses were conducted.

Overall, specificity values remained constant across subgroups; sensitivity outcomes varied considerably, especially among studies that aimed to detect any DR (category 1). For example, category 1 studies that used 7 field ETDRS fundus photographs as the reference standard showed higher sensitivity (0.96; 95%CI: 0.93-1.00) compared to their counterparts that chose slit-lamp biomicroscopy for gold standard (0.84;95%CI: 0.76-0.91). Moreover, studies that did not use pharmacologic dilation had a lower sensitivity compared to the overall calculated for the detection of any DR (0.84 versus 0.89). However, such differences in sensitivity among the above mentioned subgroups did not hold for category 2 studies (detection of referable DR). Heterogeneity did not significantly improve across subgroups. Nevertheless, studies that used 7 field ETDRS photographs as the reference standard were less inconsistent compared to the overall estimate.

Meta-regression results for each category are represented in the bubble plots (**Figure 3.6**). The magnitude of each circle is proportional to the inverse of the within-study variance of the corresponding study. Only category 1 studies (detection of any DR) showed a statistically significant association between year of publication and increased DOR (p-value 0.002).

Sensitivity analyses and publication bias

Publication bias was visually assessed by an individual funnel plot per category (**Figure 3.7**). The funnel plot is noticeably asymmetric among both categories, with missing studies at the bottom left of the graph indicating potential publication bias towards studies with positive results. For studies that detect any DR, Egger's test for small study effects was non-significant (p-value 0.072), discarding the influence of small study effects in the asymmetry of the funnel plot. In contrast, evidence of small study effects was found among studies detecting referable retinopathy (p-value 0.004).

When sensitivity analyses were performed for category 1 studies, summary sensitivity endpoints of individual studies were significantly less heterogeneous when studies with high risk of bias were excluded (Cochrane Q 8.79; P value 0.19) **(see Appendix F)**. Diagnostic accuracy and heterogeneity remained constant in category 2 studies (detection of referable retinopathy).

3.4 Discussion

3.4.1 Principal findings

Considering the quantitative summary results from the present review, it appears that tele-ophthalmology approaches meet the requested targets for an effective diabetic retinopathy screening program, as recommended by the Canadian Ophthalmological Society (sensitivity >0.80, specificity >0.90).[22,82] In category 1, which included studies with a common threshold value (detection of any DR), summary estimates showed a satisfactory diagnostic performance (sensitivity 0.89, specificity 0.94). In line with these findings, category 2 studies also showed high diagnostic performance for the detection of referable retinopathy (sensitivity 0.91, specificity 0.92). Although these are satisfactory outcomes, substantial heterogeneity was observed in both categories (Cochrane test P <0.001), limiting both the clinical interpretation and applicability of these summary estimates. Moreover, studies in category 2 do not share a common cut-off value, as studies reported different threshold definitions for the detection of referable DR. In such situation, a summary estimate calculated from the bivariate model represents an average operating point

for an average unknown threshold, which has no clinical significance.[80] The interpretation of the hierarchical SROC plot for this category **(Figure 3.5)** has greater importance as it adequately represents study information from different thresholds.[81]

Exploration of potential sources of heterogeneity is of crucial importance in systematic reviews.[48,49] Thus, we performed subgroup analyses to identify potential sources of variability previously suggested in the literature. This approach also provided the appropriate framework to explore the influence of choice of reference standard on the diagnostic performance of tele-ophthalmology programs. Among category 2, we noted that studies using a single image approach had an inferior diagnostic performance (sensitivity 0.82; specificity 0.86) compared to the overall analysis (sensitivity 0.91;specificity 0.92) These findings resonate with previous studies that used a single field photograph per eye for DR assessment and reported sensitivity values as low as 0.71.[83] With a single field photograph, pathologies at the retinal periphery may be missed, which in turn influences the rate of false negatives and affects the sensitivity of the screening test.[71,72]

We observed further differences in summary sensitivity endpoints among category 1 subgroups **(Table 3.4).** First, we observed that the choice of gold standard had some impact on the sensitivity outcomes of the index test. Studies using 7 field ETDRS photographs as the gold standard had greater sensitivity (0.96; 95%CI: 0.93-1.00) compared to studies that chose ophthalmoscopy (0.84; 95%CI:0.76-0.91). Our finding is of special importance, since 54% of included studies reported the use of ophthalmoscopy as the reference standard for the evaluation of DR screening programs, instead of the recommended gold standard by the American Telehealth Association (7 field ETDRS photographs).[6] Based on our results, researchers may take into account that the choice of ophthalmoscopy over 7 field ETDRS photographs as the gold standard may negatively affect the sensitivity performance of the index test if it aims to detect early forms of DR.

Second, meta-regression analysis found that recently published studies were associated with greater diagnostic accuracy for the detection of any DR. Such a trend

could be related to the continuous improvement of digital technologies that facilitate the identification of subtle manifestations of DR such as micro-aneurysms.

Finally in the sensitivity analysis, we found that poor methodological quality also accounts for some observed heterogeneity in pooled sensitivity results among category 1 studies. After excluding studies with risk of bias as graded using QUADAS2 criteria, we found that heterogeneity of sensitivity estimates was no longer significant (Cochran Q 8.79; P value 0.19), and inconsistency among studies was reduced to 31.7% (moderate inconsistency). However, such difference was observed only in sensitivity estimates of studies in category 1 and did not hold for studies in category 2 (referable retinopathy).

It is important to note that in all screening programs there is certain degree of harm. In the case of tele-ophthalmology, the potential harm related to the screening process itself is generally innocuous. If dilation drops are used, there is a small risk for temporal development of open angle glaucoma. However, the risk of this adverse event is very low, 1 in 20,000 cases.[87]

Adverse effects of screening are also related to the occurrence of false positive or false negative results. Patients with false positive tests undergo additional unnecessary examinations such as ocular coherence tomography or fluorescein angiography.[12] Besides the psychological distress resulting from positive results, confirmatory tests do not represent significant harm. Allergic reactions may occur due to administration of sodium fluorescein during fluorescein angiography, although serious complications are rare.[88] False negative tests may translate to missed opportunities for preventing severe vision loss.

According to our results, tele-ophthalmology screening for DR can accomplish sensitivity and specificity estimates over 80% and 95%, respectively. Such diagnostic performance is considered sufficient for supporting the early diagnosis of DR through screening programs.[88]

3.4.2 Strengths and limitations

To our knowledge, this is the first meta-analysis that evaluates and summarizes the diagnostic performance of tele-ophthalmology screening for the assessment of DR. This meta-analysis has a number of strengths. We performed a robust literature search in collaboration with an information specialist, which included a comprehensive search of major scientific databases and reference lists of reviews and articles. In addition, we selected studies according to strict inclusion criteria assessed by two reviewers; we also assessed methodological quality of studies and used two suitable statistical models for diagnostic meta-analysis in the presence of heterogeneity and different thresholds.

There are some limitations to be considered when interpreting the study results. We observed considerable heterogeneity among both study categories (Cochran Q P value <0.001), which could be explained in part by threshold effect (for category 2 studies) and poor methodological quality of some studies (for category 1 studies). According to our exploratory subgroup analysis, differences in the selection of reference standard and number of fields taken per eye may also contribute for the heterogeneity observed. However, subgroup analyses did not fully explained the variability found, as results remained heterogeneous even after stratifying by pre-defined covariates. Thus, in presence of substantial heterogeneity summary results should be cautiously interpreted. Evidence of publication bias is also a concern when interpreting summary results, as it might have an impact on study conclusions leading to overoptimistic results. However, it has been debated that in the context of reviews of diagnostic accuracy studies applying such tests for funnel plot asymmetry often lead to a high type two error rate (publication bias is incorrectly indicated by the test).[84]

This meta-analysis was also limited by lack of information provided in primary studies. We observed that almost 45% of authors did not report important population characteristics such as ethnicity, type of diabetes and diabetes duration. Reporting of visual acuity was almost non-existent, as only three authors reported visual acuity of their study population.[64,69,70] Lack of information on visual acuity

precludes any estimation of relationships between diagnostic accuracy and functional status. Similarly, some index test characteristics were also poorly reported. For example, 65% of studies did not mention the digital image resolution and 80% of studies did not provide information about image compression or image formatting. These are index technology characteristics of important relevance in image quality, which may influence the correct identification of DR cases.[85,86] Because of the limited information provided on population and digital image characteristics, future reporting of these research studies should give greater attention to provide more complete information about population characteristics, and detailed description of index technology devices. This will allow future reviews to account for these important sources of variability.

In conclusion, this systematic review with meta-analysis suggests that tele-ophthalmology tests used to assess any DR and referable DR yield satisfactory sensitivity and high specificity. Of note, diagnostic accuracy estimates amongst individual studies were highly variable, compromising the clinical significance of the meta-analysis results which in turn should be cautiously interpreted.

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3.6 Tables and figures

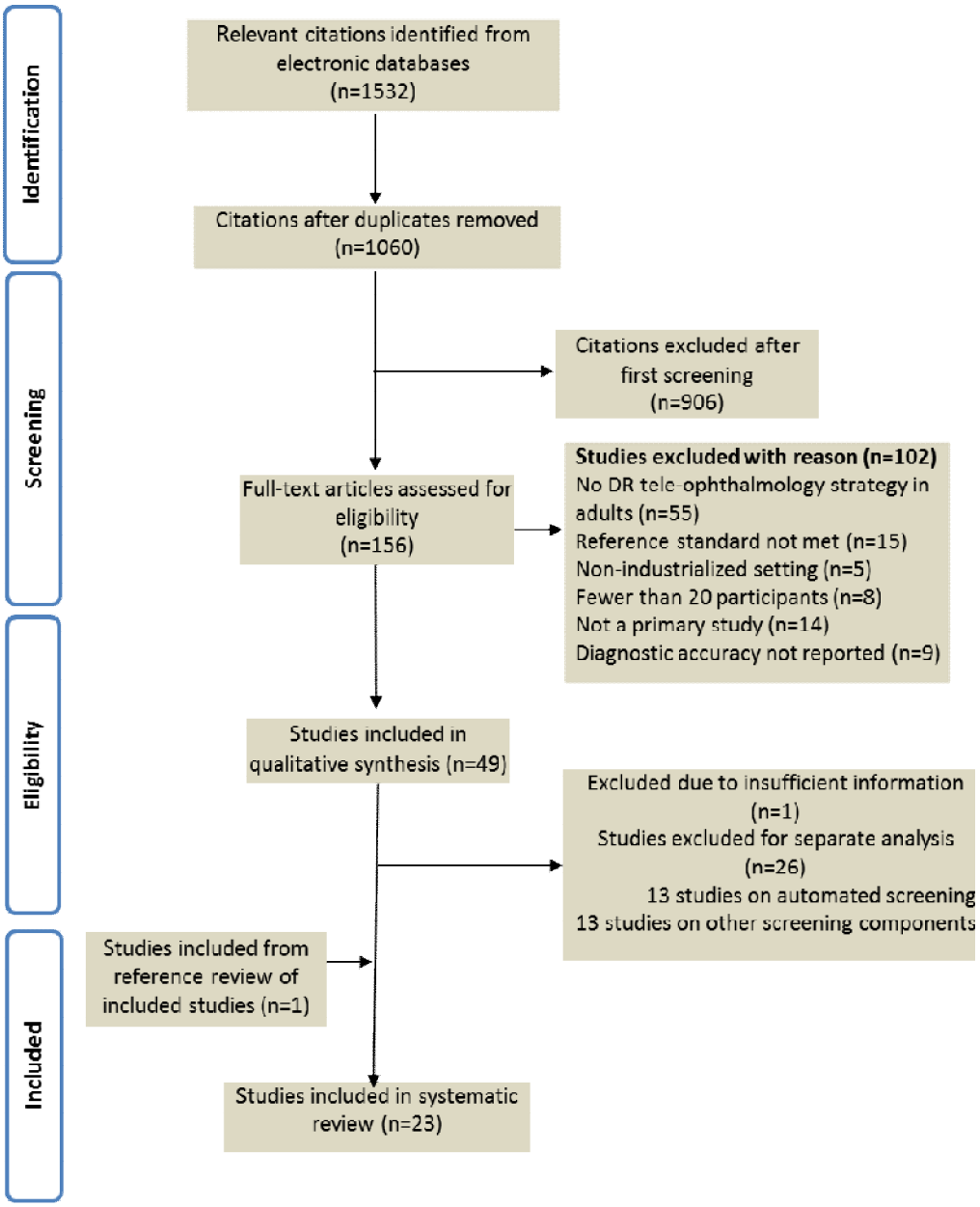

Figure 3.1 PRISMA flow diagram of study selection (systematic review)

Table 3.1. Characteristics of primary studies included in the Meta-analysis

Citation	Country	N (fully-screened)	Mean age (years)	Male (%)	Type II diabetes (%)	Gold standard	Cut-off criteria	DR prevalence
Ahmed J., et al (2006)	United States	156	60	54.5%	97.9%	Ophthalmoscopy	Any DR	15.8%*
Aptel F., et al (2008)	France	79	52.4	0.89 (men/women)	62%	Ophthalmoscopy	Any DR	25.3%
Baeza M., et al (2004)[+]	Spain	188	68.5	34.7%	100%	Ophthalmoscopy	Any DR Referable DR	41.25% 14.3%
Baeza M., et al (2009)[+]	Spain	216	68.5	43.7%	90%	7 field ETDRS photographs	Any DR Referable DR	37.2%* 14.3%
Boucher MC., et al (2003)	Canada	79	59.9	49%	NR	7 field ETDRS photographs	Any DR Referable DR	63.30% 53.10%
Chun DW., et al (2007)	United States	120	NR	50.8%	NR	Ophthalmoscopy	Any DR	32.5%*
Hansen AB., et al (2004)	Denmark	83	47	60.2%	27.0%	7 field ETDRS photographs	Referable DR	74.7%*
Herbert HM., et al (2003)	United Kingdom	145	NR	NR	73%	Ophthalmoscopy	Any DR	26.0%
Li HK., et al (2010)	United States	76	59.4	37.6%	NR	7 field ETDRS photographs	Any DR Referable DR	82.9% 77.6%*
Lin DY., et al (2002)	United States	197	NR	58.0%	NR	7 field ETDRS	Referable	36.6%*

						photographs	DR	
Lopez-Bastida J., et al (2007)	Spain	651	50.8	51.8%	NR	Ophthalmoscopy	Any DR	42.5%
Maberley D., et al (2002)	Canada	100	54.6	31.0%	NR	Ophthalmoscopy	Any DR Referable DR	40.0% 31.0%*
Massin P., et al (2003)	France	74	52	62.2%	85.13%	7 field ETDRS photographs	Referable DR	12.9%*
Molina-Fernandez E., et al (2008)	Spain	49	65.4	NR	100%	Ophthalmoscopy	Any DR	28.7%
Murgatroyd H., et al (2004)	United States	293	63 (median)	57%	65%	Ophthalmoscopy	Any DR Referable DR	37.8% 4.70%
Olson JA., et al (2003)	United Kingdom	550	56.5	65%	82.1%	Ophthalmoscopy	Any DR Referable DR	27.27% 9.9%
Phiri R., et al (2006)	Australia	149	68.5	57%	NR	7 field ETDRS photographs	Referable DR	48.6%*
Robbins AS., et al (2001)	United States	152	NR	NR	NR	Ophthalmoscopy	Any DR	18.0%
Rudnisky CJ., et al (2007)	Canada	102	59.9	65.7%	86.3%	7 field ETDRS photographs	Referable DR	4.9%
Scanlon PH., et al (2003)	United Kingdom	1542	65	NR	NR	Ophthalmoscopy	Referable DR	11.6%
Schiffman RM., et al (2005)	United States	94	57	41%	NR	7 field ETDRS photographs	Any DR Referable DR	76.10% 67.02%*

Ting DS., et al (2012)	Australia	136	53.9	NR	71%	Ophthalmoscopy	Any DR	31.3%
Vujosevic S., et al (2009)	Italy	55	57.1	60%	67.3%	7 field ETDRS photographs	Referable DR	51.4%

* Prevalence calculated from reported 2x2 tables DR= Diabetic retinopathy NR= Not reported

Ophthalmoscopy examination included slit-lamp biomicroscopy performed by experienced ophthalmologist or retina specialist

+Studies may contain overlapping patient populations

Table 3.2 QUADAS2 assessment results

Citation, year	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Ahmed J., et al (2006)	Low	Low	Low	High
Aptel F., et al (2008)	Low	High	Low	Low
Baeza M., et al (2004)	Low	Low	Low	Low
Baeza M., et al (2009)	Low	Low	Low	Low
Boucher MC., et al (2003)	Low	Low	Low	Low
Chun DW., et al (2007)	Low	Low	Low	High
Hansen AB., et al (2004)	High	Low	Low	Low
Herbert HM., et al (2003)	Unclear	Low	Low	Low
Li HK., et al (2010)	High	Low	Low	Low
Lin DY., et al (2002)	Low	Low	Low	Unclear
Lopez-Bastida J., et al (2007)	Low	Low	Low	Low
Maberley D., et al (2002)	Low	Low	Low	Low
Massin P., et al (2003)	Low	Low	Low	Unclear
Molina-Fernandez E., et al (2008)	Low	Low	Low	Low
Murgatroyd H., et al (2004)	Low	Low	Low	High
Olson JA., et al (2003)	Unclear	Low	Low	Low
Phiri R., et al (2006)	Low	Low	Low	Low
Robbins AS., et al (2001)	Low	Unclear	Low	High
Rudnisky CJ., et al (2007)	Low	Low	Low	Low
Scanlon PH., et al (2003)	Low	Low	Low	Unclear
Schiffman RM., et al (2005)	High	Low	Low	Low
Ting DS., et al (2012)	Low	Low	Low	Low
Vujosevic S., et al (2009)	Unclear	Unclear	Low	Low

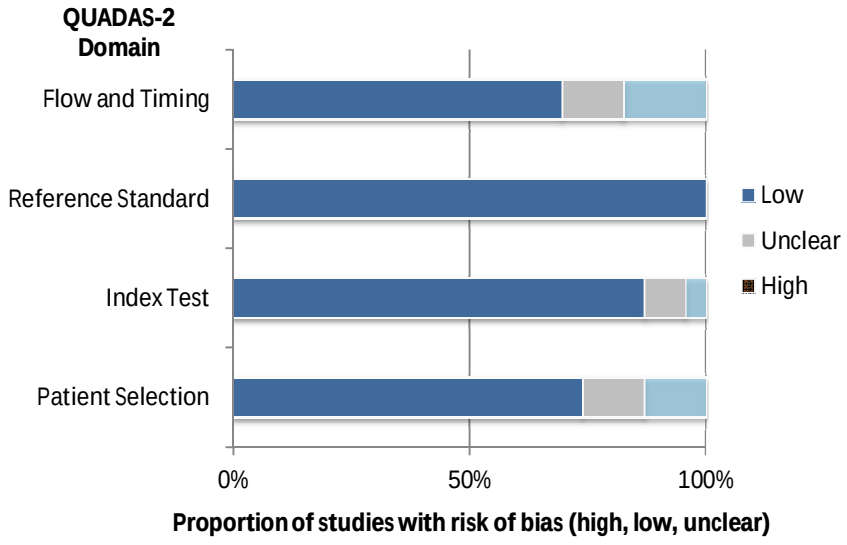

Figure 3.2 QUADAS2 assessment (risk of bias by domain)

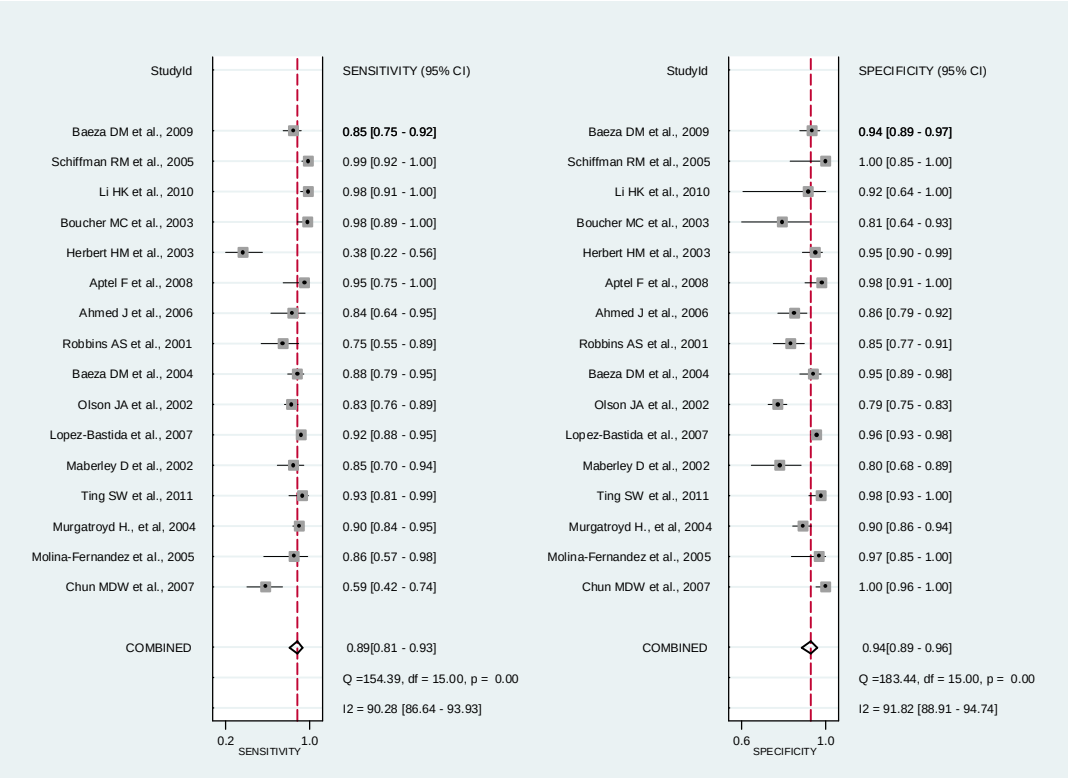

Figure 3.3. Paired forest plot of meta analyses of studies included in category 1 (detection of any DR)

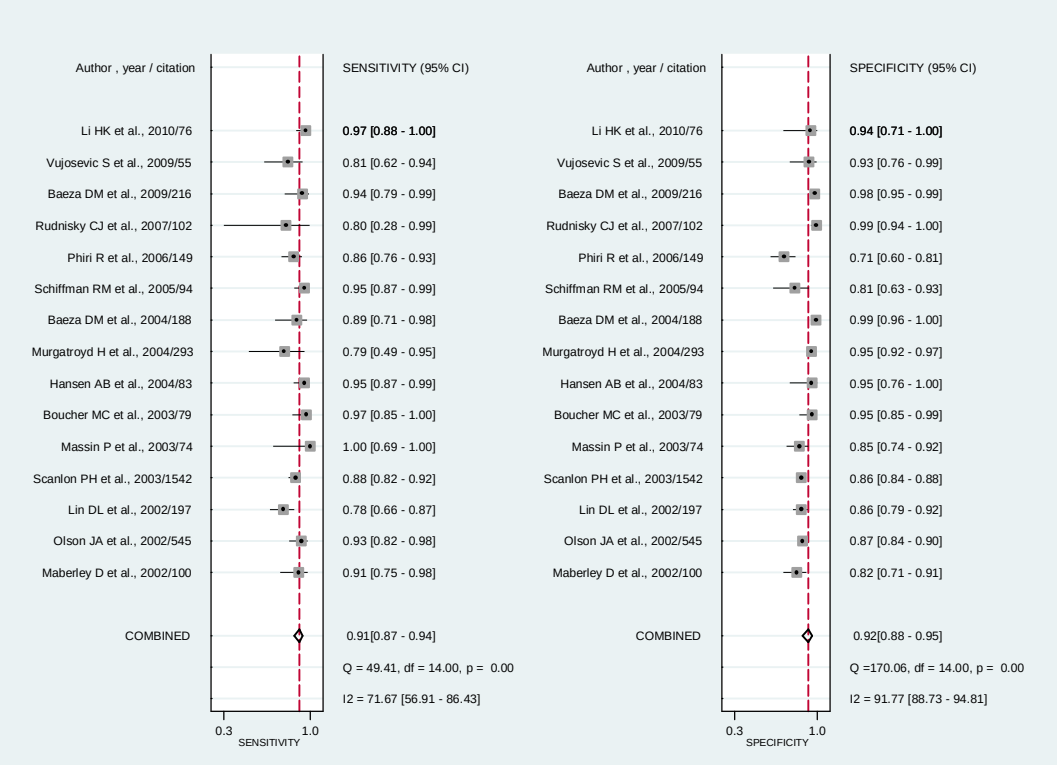

Figure 3.4. Paired forest plot of meta-analyses of studies included in category 2 (detection of referable DR)

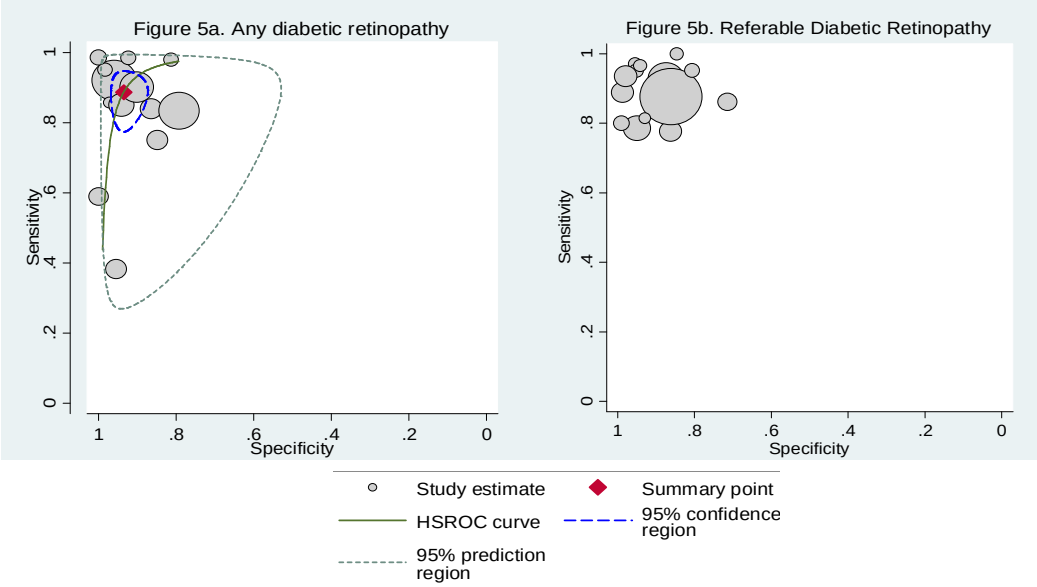

Figure 3.5 Hierarchical SROC (summary receiver operator characteristic) plots for detection of any diabetic retinopathy (**5a**), and detection of referable diabetic retinopathy (**5b**)

Table 3.3 Meta-analysis summary results per category (detection of any diabetic retinopathy and detection of referable diabetic retinopathy)

		Heterogeneity		**Diagnostic performance**				
Category	Cut-off	Inconsistency (I^2) [95% CI]	Cochran Q (Chi^2 P value)	Sensitivity [95% CI]	Specificity [95% CI]	DOR [95%CI]	LR + [95% CI]	LR - [95% CI]
Category 1 (n=16)	Any DR	96.95% [94-99]	56.3 (P <0.001)	0.89 [0.81-0.93]	0.94 [0.89-0.96]	113 [51-249]	13.8 [8.3-22.7]	0.12 [0.07-0.21]
Category 2 (n=15)	Referable DR	81.95% [60-100]	10.7 (P 0.002)	0.91 [0.87-0.94]	0.92 [0.88-0.95]	121 [58-253]	12.0 [7.1-20.1]	0.10 [0.07-0.14]

Table 3.4. Subgroup analyses of potentially relevant covariates to explore heterogeneity

	Number of studies	Heterogeneity		Sensitivity	Specificity
		Inconsistency (I^2)	Cochrane Q (Chi^2)	(95% CI)	(95% CI)
Detection of any diabetic retinopathy					
Overall analysis	16	97% (94-99)	56.3 (<0.001)	0.89 (0.81-0.93)	0.94 (0.89-0.96)
Pharmacologic dilation					
Yes/mixed	11	92% (82-100)	22.3 (<0.001)	0.91 (0.82-0.95)	0.95 (0.92-0.97)
No	4	94% (88-99)	30.4 (<0.001)	0.84 (0.66-0.93)	0.91 (0.68-0.98)
Number of fields					
Multiple	13	56% (0-100)	4.5 (0.052)	0.91 (0.88-0.95)	0.93 (0.90-0.97)
Single*	3	-	-	-	-
Gold standard					
7-field ETDRS photographs	4	72% (37-100)	6.99 (0.015)	0.96 (0.93-1.00)	0.93 (0.86-1.00)
Slit-lamp biomicroscopy	12	97% (93-99)	50.65 (<0.001)	0.84 (0.76-0.91)	0.94 (0.90-0.97)
Risk of patient selection bias					
Low risk	12	90% (79-100)	19.3 (<0.001)	0.88 (0.82-0.95)	0.94 (0.89-0.97)
Uncertain/High risk	4	95% (90-99)	38.3 (<0.001)	0.92 (0.57-0.99)	0.94 (0.78-0.98)
Detection of referable diabetic retinopathy					
Overall analysis	15	82%	10.7	0.91	0.92

		(60-100)	(0.002)	(0.87-0.94)	(0.88-0.95)
Pharmacologic dilation					
		74%	7.6	0.92	0.95
Yes/mixed	8	(42-100)	(0.011)	(0.88-0.95)	(0.88-0.98)
		60%	5.0	0.87	0.89
no	7	(10-100)	(0.041)	(0.82-0.93)	(0.82-0.96)
Number of fields					
		72%	7.2	0.93	0.94
Multiple	11	(38-100)	(0.014)	(0.89-0.95)	(0.89-0.97)
		79%	9.5	0.82	0.86
Single	4	(95-100)	(0.004)	(0.74-0.88)	(0.75-0.93)
Gold standard					
		69%	6.29	0.92	0.93
7-field ETDRS photographs	10	(29-100)	(0.022)	(0.88-0.95)	(0.88-0.97)
		77%	8.23	0.89	0.92
Slit-lamp biomicroscopy	5	(47-100)	(0.008)	(0.84-0.95)	(0.86-0.98)
Risk of patient selection bias					
		84%	12.2	0.88	0.93
Low risk	10	(65-100)	(0.001)	(0.84-0.92)	(0.87-0.97)
		0%	0.004	0.94	0.88
Uncertain/High risk	5	(0-100)	(0.499)	(0.90-0.96)	(0.85-0.90)

* Covariate analysis could not be conducted for this subgroup given the small number of studies (n <4)

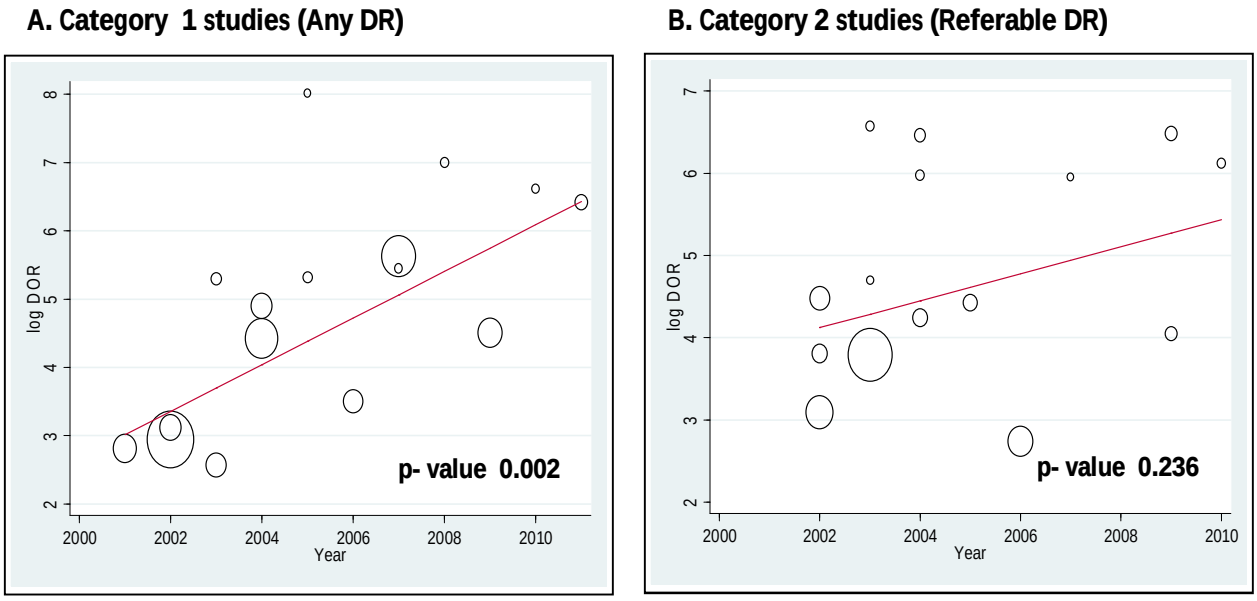

Figure 3.6 Meta-regression of log diagnostic odds ratio (DOR) on year of study (independent variable) for A. Detection of any diabetic retinopathy and B. Detection of referable diabetic retinopathy

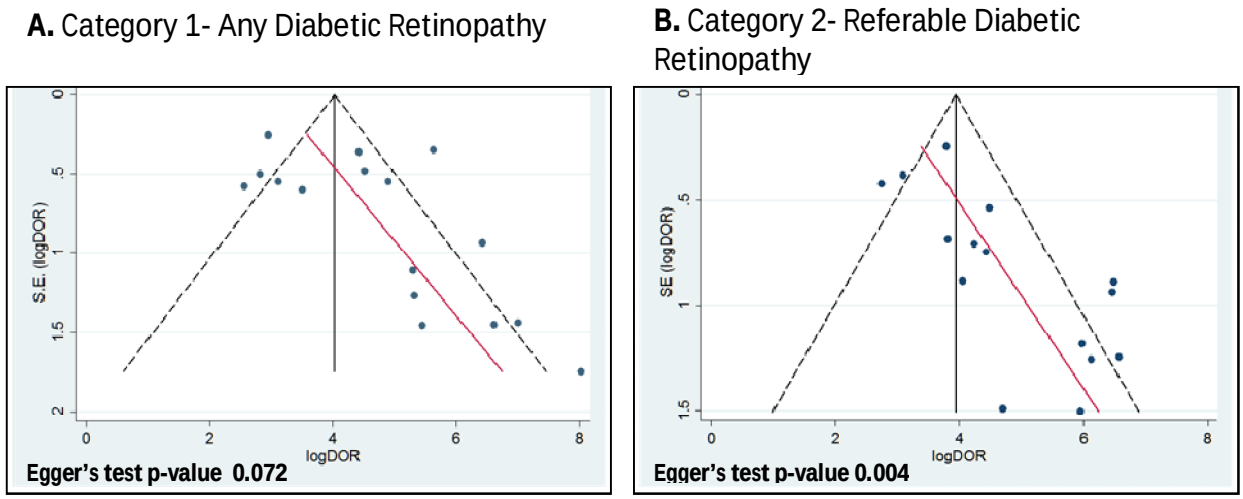

Figure 3.7 Funnel plot of standard error of log diagnostic odds ratio (logDOR) by logDOR for each study category to illustrate possible publication bias. Egger's p-value < 0.05 indicates presence of small study effects

Chapter 4 Cost-effectiveness analysis of diabetic retinopathy screening with pharmacy-based tele-ophthalmology versus in-person eye examination

Co-authorship

Coronado, AC; Zaric, GS; Martin, J; Malvankar-Mehta, MS; Hodge, WG

4.1 Introduction

Diabetic retinopathy (DR) is a sight threatening complication in patients with diabetes mellitus, and is usually asymptomatic in early stages[1–3]. According to recent investigations, 2.5% of diabetic patients worldwide suffer severe vision loss derived from DR, being this the leading cause of blindness among working-aged individuals.[4,5] Regular eye examination is fundamental to detect DR progression and to promote timely therapeutic interventions.[6] Laser photocoagulation for example, is an effective treatment for DR with 52% of patients experiencing reduction of severe vision loss if they receive treatment after timely diagnosis of sight-threatening DR.[7,8]

Unfortunately, less than 50% of diabetic patients follow the eye examination guidelines by the American Academy of Ophthalmology[9], resulting in lost opportunities to prevent severe vision loss by means of adequate treatment delivery.[5,10,11] Besides non-modifiable factors, limited availability of eye care specialists, travelling difficulties and time constraints are also well-known reasons for non-adherence in non-urban areas.[12–15]

Within this context, pharmacy-based tele-ophthalmology has emerged as a possible alternative that may facilitate compliance with evidence-based recommendations and reduce barriers to specialized eye care.[16–18] In this program, retinal digital images are captured in a local pharmacy and securely transmitted electronically to a specialized reading centre, where photographs are graded by an eye specialist.[19] Patients with signs of DR can then be referred to an eye-care professional for comprehensive assessment.[20] Thus, the workload of routine eye examination is transferred to other (presumably less expensive) settings, optimizing the use of specialized eye-care services. In addition, this approach eliminates unnecessary traveling for patients and eye care professionals, and it may improve the consistency of community-based eye care delivery without geographic constraints.[17,21]

Cost-effectiveness of new technologies should be explored before implementation in specific settings in order to facilitate estimation of the eventual costs of introducing new technologies, as well as their potential benefits compared with competing alternatives.[22] Amongst cost-effectiveness studies conducted in the DR screening arena, few have evaluated tele-ophthalmology as an alternative for in-person examination.[23–27] Thus, the objective of this study was to estimate the cost-effectiveness of mobile tele-ophthalmology screening compared to primary care examination for the diabetic population residing in non-urban areas of Southwestern Ontario (Canada). Our primary interest was to assess the additional cost per case detected of any diabetic retinopathy with pharmacy-based tele-ophthalmology on an annual basis from the health system perspective. Unlike previous studies, we consider a more realistic scenario in which the tele-ophthalmology program would not entirely replace in-person examination, while also accounting for the effects of performing a dilated or non-dilated examination with tele-ophthalmology.

4.2 Methods

4.2.1 Study setting

The economic analysis was designed for the South-western Ontario context, specifically non-urban areas at the Erie-St. Clair Local Health Integration Network (LHIN).[28] Such non-urban areas have limited specialized eye-care and diabetic care, in which a pharmacy-based tele-ophthalmology system may be of benefit, as it would help reaching diabetic individuals who otherwise would not get an eye examination.[29] As of 2011, the census subdivision contemplated in this study (Chatham-Kent) reported a total of 103,671 habitants (population density of 14.2 people per km^2), from which 10,354 are type I or type II diabetic persons over 20 years old.[30,31] An explicitly urban model (ie Toronto) was not chosen based on the assumption that in-person exams would be relatively easy to access in this setting. An explicitly rural model (Canada's far north) was not chosen since tele-ophthalmology may be the only alternative in such

locations. However, there is true equipoise in understanding the cost-effectiveness of this program in a context such as the Erie-St Clair LHIN.

4.2.2 Decision-tree model and study interventions

A decision-tree was elaborated using TreeAge Pro Suite 2013 (TreeAge Software, Inc, Williamstown, Massachusetts), to compare primary care examination (comparator program) versus pharmacy-based tele-ophthalmology (intervention program). [32] A simplified diagram of the decision-tree is provided in **Figure 4.1** (for the full model, refer to **appendix G**). In the analytical framework, we assumed that the pharmacy-based tele-ophthalmology program coexisted along with the reference program, increasing the volume of DR examinations (Figure 4.1, arm 2) but did not entirely replace in-person examination. This assumption aligns to the purpose of the tele-ophthalmology program to complement existing eye-care services.

The model was tailored for a mixed cohort of adults with type I or type II diabetes. The outcome of interest was the detection of any diabetic retinopathy, manifested by at least one micro-aneurysm (ETDRS ≥ 20).[33] This health outcome was chosen based on the goal of identifying both early and advanced stages of DR, which would promote an appropriate follow-up or timely treatment, if necessary.

Our interest focused on the potential ability of pharmacy-based tele-ophthalmology to strengthen diabetic retinopathy screening coverage at a reasonable cost. Thus, our analysis was restricted to the correct detection of DR cases, as opposed to incorporating treatment effects and disease progression into the model. A heath care system perspective was adopted, where consequences and direct costs pertaining to each program were included based on a 12-month time frame.

Intervention: Pharmacy-based tele-ophthalmology

The economic model was designed for the evaluation of a category 1 tele-ophthalmology screening program, used to identify patients with no (or minimal) DR

and patients with more than minimal DR.[16] We considered the introduction of a part-time mobile retinal unit, operating on a rotational basis among regional pharmacies at the main municipalities of Chatham-Kent. In this model, clinical history and 45 degree digital photographs were taken from each eye by an ophthalmic photographer and pharmacologic dilation with tropicamide or phenilephrine was optional. Readable digital images were sent via electronic communications to the reading center at St. Joseph's hospital in London (ON) for assessment by a retina specialist. Patients with positive findings were referred to a retina specialist for a diagnostic confirmation with angiography and optical coherence tomography. Similarly, patients with unclear fundus photographs were referred to in-person examination with the retina specialist for further assessment.

Comparator: In-person examination (primary care)

The primary care screening was defined as a dilated fundus examination performed by a primary care eye specialist (either an optometrist or ophthalmologist). Patients with positive results were referred to a retina specialist for a comprehensive eye examination with angiography and optical coherence tomography.

4.2.3 Identification and calculation of model probabilities

Probabilities used in the base-case model are shown in **Table 4.1**. Prevalence of any DR (22.5%) was calculated using public reports by the Public Health Agency of Canada and the National Coalition for Vision Health.[34,35] Screening rate with the reference program in Arm 1 ($P_{(ref)}$) was considered to be identical to the eye examination rate after diagnosis of diabetes in Ontario (51.1%).[36] After the introduction of the new screening intervention (appendix G, Arm 2), the patient had two screening alternatives (in-person examination or telescreening) and would choose according to preference for one or the other. The option of no screening was also included in both arms of the model. Hence, to calculate the screening rate of tele-ophthalmology examinations ($P_{(tele)}$), we used the following formula that considered the increased screening compliance after the

introduction of tele-ophthalmology (V) and the proportion of screening examinations with tele-ophthalmology based on screening preference (T), as follows

$$\mathbf{P_{(tele)} = T\,(\,P_{(ref)} \times V\,)} \quad , V \geq 1,\ P_{(tele)} < 1 \qquad (1)$$

In this equation, "$P_{(ref)}$ x V" is the overall screening rate for Arm 2, and "$P_{(tele)}$" is the proportion of those examinations from Arm 2 that correspond to tele-ophthalmology screening**.**

Both patients' preferences (T) and screening compliance after tele-ophthalmology (V) were derived from published literature. For this purpose, a structured literature search was performed among Medline and EMBASE databases using the subject headings "telemedicine", "mobile health units", "mass screening", "early diagnosis", "community pharmacy service" (**appendix H**). Priority was given to studies from primary care screening services using mobile screening units in urban or semi-urban settings. For the base-case model, the volume increase in DR examinations after tele-screening (V) was set to 10%, with 40% of patients favoring pharmacy-based telescreening examination over the comparator.[18,37,38] Hence, the base-case screening probability for the tele-ophthalmology arm (Figure 4.1, Arm 2) was 0.562. For detailed calculations of model probabilities, refer to **appendix I**.

Estimates of the diagnostic performance of tele-ophthalmology were obtained from a recent meta-analysis[39] that separately reported the summary results according to diagnostic threshold. Therefore, we used the summary sensitivity and specificity corresponding to the assessment of any DR, and derived the diagnostic performance of in-person examination from one of the included studies.[40] We also used this data to calculate the proportion of unreadable images with tele-ophthalmology with and without pharmacologic dilation. Finally, the proportion of dilated examinations was obtained from a study that used pharmacy-based tele-ophthalmology for DR screening across Canadian provinces.[41] It was assumed that pupil dilation with tropicamide or

phenylephrine was performed by the pharmacist at the patient's discretion. All probabilities used in the economic model are outlined in **appendix J**

4.2.4 Identification and calculation of model costs

Data sources for estimates of costs included published literature, market prices, vendor's quotations, official government reports and administrative information from St. Joseph's Healthcare in London (ON). Only direct costs were incorporated into the model and presented in 2013 Canadian dollars.

Cost information is provided in **Table 4.2**. Equipment for the tele-ophthalmology program consisted of a non-mydriatic digital fundus camera, a carrying case, an adjustable table, a laptop and reading software. Costs related to equipment and maintenance were obtained directly from the vendor and was given a 5 year life (written communication, 2013). Capital costs were annualized at a 5% discount rate per year, corresponding to the rate for Ontario government bonds.[42] In contrast, capital costs for in-person examination were not included, as the ophthalmoscope and lens are already bought and routinely used for any eye examination.

Traveling costs of the mobile retinal unit consisted on van rental cost (including insurance) and fuel expenses for traveling across the Chatham-Kent municipality. Rental costs estimates were provided from the vendor; fuel costs were obtained from the Ontario Ministry of Energy report and reflected the cost per gallon in Ontario.[43] Pharmacy overhead costs were calculated from the annual Pharmacy Trends Reports, which provided information on annual operating expenses per square foot among Canadian pharmacies.[44] Thus, we adjusted the cost to the part-time use of pharmacy space in 2013 Canadian dollars.

Technician costs for tele-ophthalmology were based on current prevailing wages provided by administrators at St. Joseph's Hospital in London (written communication, 2013). To estimate the labor cost per patient assessment, a structured literature search was conducted with Medline and EMBASE to find economic studies on DR screening

that reported information on average minutes of labor cost per patient. Subject headings included “diabetic retinopathy”, “diagnostic imaging”, “cost allocation”, “healthcare costs” (**appendix K**). Six studies calculated the average minutes spent by personnel for taking and/or assessing eye photographs, which varied between 5 and 15 minutes.[24,45–49] Based on this information, we extrapolated the cost per hour of technician labour to the cost per patient assessment with the tele-ophthalmology program.

In-person consultation fees for major eye examination were obtained from the Schedule of Benefits of Physician Services by the Ontario Ministry of Health and Long-term care.[50] The ophthalmic reader fee was based on the tele-consultation fee provided by the Alberta Healthcare Insurance Plan for pediatricians and related subspecialties.[51] It was assumed that an Ontario tele-consultation fee for DR assessment would resemble that of Alberta for tele-consultation in pediatric specialties. Patient referral costs and consumables costs were obtained from vendors’ quotations and administrative information from St. Joseph’s Health Care (London, ON).

4.2.5 Cost-effectiveness evaluation and sensitivity analysis

Two measures of effectiveness were analyzed in this study; (1) cases of any DR detected (true positives) and (2) cases correctly diagnosed (including true positives and true negatives). A case of DR was defined as any DR beyond very mild non-proliferative DR, corresponding to a Modified Airlie House Classification ≥20 on the reference standard.[33] Cost- effectiveness was calculated as total cost divided by number of cases detected (or number of cases correctly diagnosed). Thus, the Incremental Cost Effectiveness Ratio (ICER) was calculated as the extra cost needed to generate (1) an additional case of DR or (2) an additional case correctly diagnosed after the implementation of pharmacy-based tele-ophthalmology.[52]

Deterministic Sensitivity Analysis

Parameters considered as potential drivers of the model were included in sensitivity analysis, and were assigned plausible ranges based on 95% confidence intervals or upper and lower 25% limits around the base-case value. For simplicity we limited the reporting of sensitivity analyses to the cost per case detected per year.

One way sensitivity analyses were conducted for most data elements to investigate the extent to which each variable's uncertainty affected the model results. Variables considered for one-way sensitivity analysis with their respective ranges are listed in **Table 4.1** (model probabilities) and **Table 4.3** (model costs). A multi-way sensitivity analysis was also performed, where model parameters were varied simultaneously to generate extreme scenarios.

4.3 Results

4.3.1 Base-case analysis

In the base-case analysis we considered a tele-ophthalmology program that achieved a 10% volume increase in patient compliance, with a 0.18 probability of unreadable images and pharmacologic dilation in 33% of examinations. Considering a population of 10,354 diabetic patients, the tele-ophthalmology program would correctly detect additional 136 cases compared to in-person examination only (**Table 4.4**). Cost-effectiveness was assessed as (1) cost per case detected, and (2) cost per case correctly diagnosed. For (1) the cost-effectiveness of in-person examination and tele-ophthalmology was $510 and $478.3, respectively, whereas for (2) was $107 for in-person examination and $73.2 for tele-ophthalmology. The incremental cost-effectiveness (ICER) was $314.1 per additional case detected and $102 per additional case correctly diagnosed (**Table 4.5**). In both instances the programs were non-dominant; hence, tele-ophthalmology was always more costly, but more effective than in-person examination. (**Figure 4.2**).

4.3.2 Sensitivity analyses

Sensitivity analyses assessed uncertainties of model parameters, including diagnostic accuracy, DR prevalence, compliance and costs. Results of multiple one-way sensitivity analyses are outlined in **Table 4.6**. We found that the model was stable with regards to sensitivity, specificity and prevalence variations. Similar to a previous study,[53] workforce wages played a significant role in the cost-effectiveness of both screening programs. In the case of tele-ophthalmology, we observed that the ICER doubled its base-case value when the image reader's fee (retina specialist) increased from $31.6 to $55.4 per patient. This parameter is an important source of uncertainty since Ontario currently does not have a tele-ophthalmology code that could serve as a reference for the model. For the base-case scenario we used a proxy code from the Alberta Schedule of Medical Benefits (code 03.05JJ).[54] This code is used by pediatricians (including subspecialties) if they provided a five minute evaluation or consultation by telephone or other telecommunication methods, which is similar to the service a retina specialist would provide in a category 1 tele-ophthalmology program.

Conversely, if the in-person examination fee increased from $51.1 to $78 per person, tele-ophthalmology program dominated at a cost of $603 per true positive case detected compared to $737 per case detected with in-person examination.

Other influential variables in the tele-ophthalmology program included the proportion of unreadable images (without pupil dilation) and the grader fee. When the proportion of unreadable images increased to 0.43, the ICER also increased to $411.2 per additional case detected per year. Similarly, when the tele-ophthalmology grader fee per patient incremented up to 25%, the ICER also increased to $633.9 per additional case detected per year.

A two-way sensitivity analysis was conducted to estimate the joint influence of screening volume and patients' preferences on the cost-effectiveness of pharmacy-based tele-ophthalmology. As expressed in equation (1), both parameters were used to calculate the screening rate for both programs under the assumption that the two

screening alternatives were available to the patients after the introduction of tele-ophthalmology (Arm 2). We defined a tele-ophthalmology preference range from 10% to 100% and considered a volume increase of 10% (base-case) 15% and 20%. Tele-ophthalmology remained non-dominant in all combinations (**Figure 4.3**). Of note, the lowest ICER was achieved when all screened patients used pharmacy-based tele-ophthalmology ($192 per additional case detected per year).

In the extreme scenario analyses, both costs and probabilities were manipulated to generate alternative settings that would represent the best and the worst scenario for the introduction of pharmacy-based tele-ophthalmology. In the best-case scenario, influential parameters were defined as follows: patient preference for tele-screening increased to 0.70 (assuming all patients had a dilated examination), tele-screening diagnostic performance was defined according to upper 95% confidence intervals for sensitivity and specificity (Se 91%, Sp 97%), while in-person examination was set to its lowest diagnostic performance (Se 67% Sp 79%). Also, the rate of unreadable images for tele-ophthalmology was fixed at its lowest value (3.3%). Finally, fees corresponding to the tele-ophthalmology coordinator, ophthalmic photographer and the retina expert grading were reduced by 15% ($20.5, $20.5 and $23.75 respectively). We found that tele-ophthalmology dominated at $367.6 per case detected per year, being less costly and more effective than in-person examination ($575.1 per case detected per year).

Alternatively, the worst case scenario was fixed under the poorest diagnostic performance for tele-screening (Se 76%; Sp 90%) and the best sensitivity and specificity values for in-person examination (Se 83%; Sp 86%), the highest rate of unreadable images (43.5%) and a 15% increase in the coordinator, eye photographer and retina expert fee ($34.21, $34.21 and $55.21, respectively). In this scenario, tele-ophthalmology remained undominated although the incremental cost-effectiveness was four times higher than the base-case ($1,393 per additional case detected per year).

4.4 Discussion

4.4.1 Cost-effectiveness of tele-ophthalmology

The detection of DR by means of tele-ophthalmology programs has proven to be a cost-effective alternative amongst isolated communities, generating savings through lower transportation and personnel costs.[17,25] In terms of total annual costs, the introduction of tele-ophthalmology was more expensive than in-person examination but detected 15% more cases of any DR at $314.1 per additional case. In the Chatham-Kent context, this was translated to 528 more patients attending eye examination, and 136 additional DR cases detected.

A previous study assessed the cost-effectiveness of systematic photographic screening versus opportunistic eye examination in the UK.[46] Adjusted to 2013 Canadian dollars, the incremental cost per additional DR case detected was $83, which was regarded as cost-effective within the British healthcare system. In comparison, the incremental cost-effectiveness of tele-ophthalmology may be too high to consider its implementation in a semi-urban context. However, if an exclusive use of tele-ophthalmology is assumed, the ICER would be reduced to $192 per case detected, almost half of the base-case value and closer to the acceptable cost-effectiveness estimate reported by James and colleagues.[46]

4.4.2 Sensitivity analyses

Sensitivity analyses showed an important influence of healthcare specialists' fees for in-person examination and interpretation of retinal images. As expected, the ICER increased as the fee of retinal image readers increased up to 15% its base-case value. Alternatively, when in-person examination cost reached $78 per patient, tele-ophthalmology became less costly and more effective, dominating over in-person examination.

Undilated tele-screening examinations showed a higher rate of unreadable images, which affected the incremental cost-effectiveness of the program. Although pupil

dilation may improve image quality and lower the costs, it may prevent patients for getting screened at the pharmacy, as reported in previous studies.[41,55] Hence, the option of including pharmacologic dilation will depend on the overall goal of the tele-ophthalmology program.[16] For example, if the primary concern is to assess more patients, then a program without pharmacologic dilation would be convenient, at the expense of increasing the proportion of unreadable images.

4.4.3 Comparison to previous evidence

In contrast to our findings, other studies have reported tele-ophthalmology to be highly cost-effective or even dominant at the base-case analysis.[24,56,57] However, comparisons of our results with prior published studies are not straightforward due to differences in effectiveness outcomes and model assumptions. For instance, Whited and collaborators used data from three US agencies to build nine economic models based on the Joslin Vision tele-ophthalmology system.[24] Tele-ophthalmology dominated clinic-based ophthalmoscopy in seven models, and was cost-effective at extra $1,618 (2004 US dollars) per additional case treated in the remaining two models. In contrast to our model, this study assumed an exclusive initial use of the tele-ophthalmology alternative, and its diabetic population was eight to twenty times bigger than in Chatham-Kent, assuring maximum efficiency of both labor and equipment.

In the Canadian context, Maberley et al.,[25] evaluated the introduction of a tele-ophthalmology system in a First Nations community, where retina specialists traveled twice a year to make eye-examinations. Similarly, Aoki et al., assessed the introduction of a tele-ophthalmology program in a remote US prison versus current practice consisting on sporadic eye examinations by eye specialists.[56] Both studies assessed the cost-effectiveness of an alternative tele-ophthalmology program in terms of quality-adjusted life-years (QALY), and found tele-ophthalmology to be dominant over current practice.[25,56] The context in which these studies were framed differs greatly from the semi-urban scenario used in our model, as they assumed an exclusive use of the tele-ophthalmology program. Costs of in-person examinations are superior in remote areas,

as usually includes transportation costs of either patients or healthcare personnel to meet eye-screening needs. Hence, the capital cost of the tele-ophthalmology program is by far justified in isolated communities through lower personnel and transportation costs.

4.4.4 Strengths and limitations

To our knowledge, this is the first study that models the introduction of a tele-screening program in a semi-urban population without considering exclusive initial use of this technology. Although the exclusivity assumption is commonly used in cost-effectiveness analyses, it is very unlikely that a new tele-ophthalmology program would entirely replace in-person examination in a context where primary care professionals are permanently available.[18,19] We also contemplated key variables of tele-ophthalmology systems such as need for pharmacologic dilation and rate of unreadable images, and evaluated their influence on the cost-effectiveness of a category 1 tele-ophthalmology program.[16]

Our model has some limitations worth noting. First, the present study was tailored to the Chatham-Kent community. Patient pool size and prevalence was captured from provincial reports; costs were derived from provincial information and administrative data from St. Joseph's healthcare in London (ON). Although aligned with the study objectives, such specificity limits the applicability of these results to other settings. However, the model structure of this analysis can be used in upcoming studies for the evaluation of DR screening programs in similar geographic contexts. Second, the study was conducted from a healthcare payer perspective, and indirect costs were not included. Nonetheless, a societal perspective would likely favor the implementation of tele-ophthalmology due to the inclusion of travel costs avoided and reduced time away from work.[59] Third, we used number of true positive cases detected (and number of cases correctly diagnosed) as our effectiveness outcome. Although this is a clinically intuitive measure that provides useful insight regarding the comparative cost-effectiveness of interventions, it does not reflect the full effectiveness of the program as

it does not take into consideration the therapeutic endpoint (e.g cases of blindness averted, prevention of SVL). It also limited the direct comparison of our results with other studies that used preference-based measures (e.g QALYs).

4.4.5 Study applicability

This study opens the discussion as if the benefits of mobile tele-ophthalmology in semi-urban areas are equivalent to those benefits observed in remote populations. In a semi-urban community, the implementation of tele-ophthalmology would be almost three times more expensive compared to a context where the tele-ophthalmology program is assumed to be exclusive. Although our results suggest increased benefits of tele-ophthalmology versus in-person examination in terms of more patients being screened and additional DR cases being detected, the incremental cost of $314 per case may be considered too high to be implemented in a publicly funded healthcare system. This is largely due to the fact that the healthcare payer would still have to support in-person examination in addition to the new telescreening program, especially during early stages of program execution.

If stakeholders are interested in investing on a telescreening program in a semi-urban context, a comprehensive discussion about potential strategies to reduce screening costs should be in order.[60] From the sensitivity analyses, we found that eye specialist fees and pupil dilation are the most influential factors in the cost-effectiveness of the tele-ophthalmology program. Given that pharmacologic dilation reduces the proportion of unnecessary referrals due to unreadable images, a program with pupil dilation to all patients will improve cost-effectiveness. Also, the automated detection of DR lesions is an alternative to the manual assessment of digital images by a specialist.[61]

It is worth noting that our interpretation is based on the incremental cost per case detected. Clinical outcomes such as cases of SVL averted or cases of blindness prevented were out of the scope of this study. Economic studies based on rural communities have found an increased benefit of tele-ophthalmology in terms of clinical outcomes and quality of life.[25,47,62,63] It is possible that tele-ophthalmology may offer great benefits in

terms of cases of SVL averted or QALYs in a semi-urban context, which would justify the initial investment in equipment and labor. Further studies should expand on the analysis based on these important clinical endpoints to gain a better understanding about the overall benefits of tele-ophthalmology in the semi-urban context.

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4.6 Tables and figures

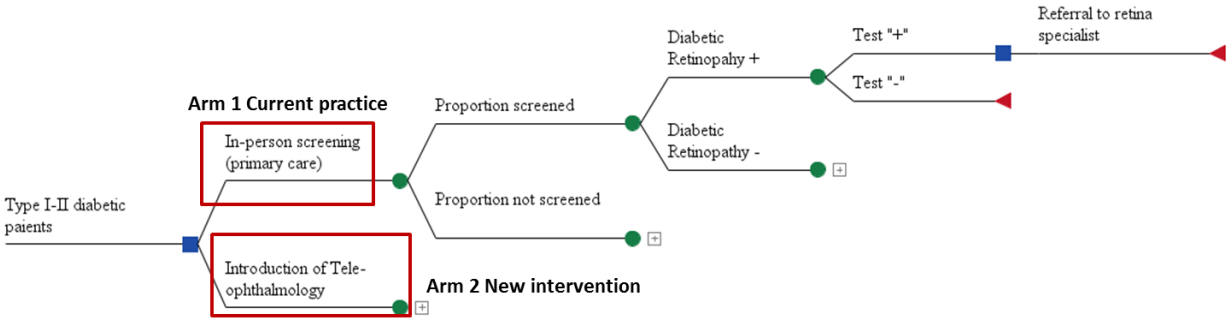

Figure 4.1 Illustration of a portion of decision tree showing competing alternatives for diabetic retinopathy screening. Arm 1 corresponds to current practice (in-person examination); Arm 2 corresponds to the new intervention evaluated in the model (pharmacy-based tele-ophthalmology)

Table 4.1. Base case model parameters and parameter ranges

Parameter	Value	Range (interval for DTA)	Source
Fixed Data Elements			
Diabetic population in study setting	10,354 patients	-	Booth GL et al, 2012
Eye examination rate with current practice	0.511	-	Buhrmann, Assaad, Hux, Tang, & Sykora, 2003
Volume increase of screening compliance after tele-ophthalmology is implemented	10% increase	-	Olayiwola et al., 2011; Vargas-Sánchez, Maldonado-Valenzuela, Pérez-Durillo, González-Calvo, & Pérez-Milena, n.d
Variable Data Elements			
Prevalence of any DR in Canada	0.225	0.169 to 0.281	National Coalition for Vision Health, 2007; Public Health Agency of Canada, 2011
a) Screening intervention parameters (tele-ophthalmology)			

Proportion prefers tele-ophthalmology for DR screening	0.40	0.50; 0.60; 0.70	Leese, Newton, Jung, Haining, & Ellingford, 1992; Taylor et al., 2007; García Serrano et al., n.d.
Proportion examined with tele-ophthalmology*	0.225	0.169 to 0.281	Leese, Newton, Jung, Haining, & Ellingford, 1992; Taylor et al., 2007
Sensitivity	0.84	(95% CI) 0.76 - 0.91	Coronado et al., 2013
Specificity	0.94	(95% CI) 0.90 - 0.97	Coronado et al., 2013
Proportion of dilated examinations	0.337	(95% CI) 0.25-0.47	Boucher et al., 2008
Proportion of unreadable images with pupil dilation	0.054	(95% CI) 0.033-0.076	Coronado et al., 2013
Proportion of unreadable images without pupil dilation	0.287	(95% CI) 0.139-0.435	Coronado et al., 2013
b) Current practice parameters (in-person examination)			
Proportion examined with current practice (Pc) after introduction of tele-ophthalmology*	0.337	0.253 to 0.421	Leese, Newton, Jung, Haining, & Ellingford, 1992; Taylor et al., 2007
Sensitivity	0.75	(95% CI) 0.67-0.83	Olson et al., 2003
Specificity	0.82	(95% CI) 0.79-0.86	Olson et al., 2003

DTA=Deterministic sensitivity analysis; DR=Diabetic Retinopathy

* Based on published data estimates about proportion of patients screened after introduction of tele-ophthalmology and patient preferences towards examination with tele-ophthalmology. For detailed calculations refer to Appendix I

Table 4.2 Estimated costs for in-person examination and pharmacy-based tele-ophthalmology

Item	Cost per unit	Unit description	Total cost	Data source
*Capital costs**			*Cost/year*	
Digital Camera	$ 17,458.50	One retinal camera	$ 4,032.45	Vendor's quotation
Table Lift	$ 1,045.25	One table lift	$ 241.43	Vendor's quotation
Software	$ 1,610.25	One software package	$ 371.93	Vendor's quotation
Carrying case	$ 1,299.50	One carrying case	$ 300.15	Vendor's quotation
Maintenance	$ 460.00	Annual	$ 460.00	Vendor's quotation

			maintenance			
Camera transportation costs					*Cost/year*	
Van rent	$	91.07	One cargo van	$	1,092.84	Vendor's quotation
Fuel	$	1.27	One litre	$	76.26	Ontario Ministry of Energy, Ontario prices 2013
Overhead costs†					*Cost/year*	
Pharmacy overhead costs	$	155.00	Annual expenditures per square foot	$	775.00	10th annual Pharmacy Trends Report, 2004
Labour costs					*Cost/patient*	
Tele-ophthalmology coordinator	$	24.18	Hourly wage[£]	$	4.03[ϕ]	St. Joseph's Hospital administrative data
Photographer	$	24.18	Hourly wage[£]	$	6.05[ϕ]	St. Joseph's Hospital administrative data
Grader (ophthalmologist)	$	31.66	Consultation per patient	$	31.66	Alberta Healthcare Insurance plan
Eye care specialist	$	51.10	Consultation per patient	$	51.10	Ontario Ministry of Health and Long-term Care
Consumables					*Cost/patient*	
Referral to retina specialist	$	111.31	Examination per patient	$	111.31	St. Joseph's Hospital administrative data
Dilation drops-Tropicamide 1%	$	16.15	Cost per unit (15 ml)	$	0.54	St. Joseph's Hospital, pharmacy data
Dilation drops-phenylephrine 2.5%	$	4.82	Cost per unit (5 ml)	$	0.120	St. Joseph's Hospital, pharmacy data
Chin covers	$	56.50	Cost per pack (500)	$	0.113	Vendor's quotation

*Annualized based on a 5-year life equipment and a 5% depreciation rate

†Based on average annual pharmacy overhead expenditures for 5 square feet, adjusted to inflation

[£]Based on a part-time annual salary of $21,762.

[ϕ]Part-time salary was extrapolatedaccording to the number of patients per hour. Workload estimation was defined based on literature searches (see appendix K)

Table 4.3 Cost ranges used for Deterministic Sensitivity Analysis

Item	Unit description	Cost		Value or Range† (for DSA)
Capital costs				
Digital Camera	One retinal camera	$ 17,458.50	$	29,798.10
Labour costs				
Tele-ophthalmology coordinator	Consultation per patient	Hourly wage		$24.18
Photographer	Consultation per patient	Hourly wage		$24.18

Grader (ophthalmologist)	Consultation per patient	$	31.66	$ 23.75 to $ 55.41
Eye care specialist	Consultation per patient	$	51.10	$ 38.33 to $ 89.43

† Range based on upper and lower 25% limits

Table 4.4 Examination outcomes of pharmacy-based tele-ophthalmology and in-person examination programs per 10,354 diabetic patients in the study model

	In-person examination	**Introduction of tele-ophthalmology**
Patient compliance (%)	51.1%	56.2%
True positive	893	1029
True negative	3362	3914
False positive	738	595
False negative	298	280
Total patients screened	5291	5819

Table 4.5 Incremental cost-effectiveness results for in-person examination versus introduction of tele-ophthalmology

Screening stategy	Cost per patient	Incremental cost per patient	Effectiveness (case detected)	Incremental effectiveness	ICER	Dominance
In-person screening (primary care)	$43.98		0.086			Undominated
Introduction of Tele-ophthalmology	$49.22	$5.24	0.103	0.017	**$314.1**	Undominated

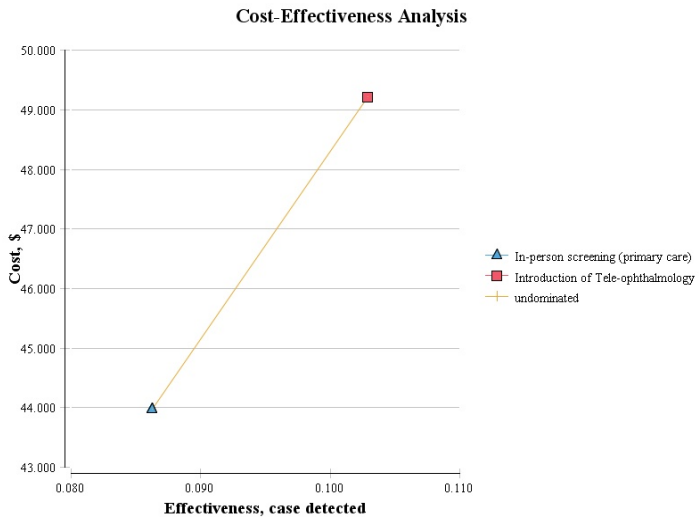

Figure 4.2 Cost-effectiveness plane. In-person examination versus introduction of tele-ophthalmology

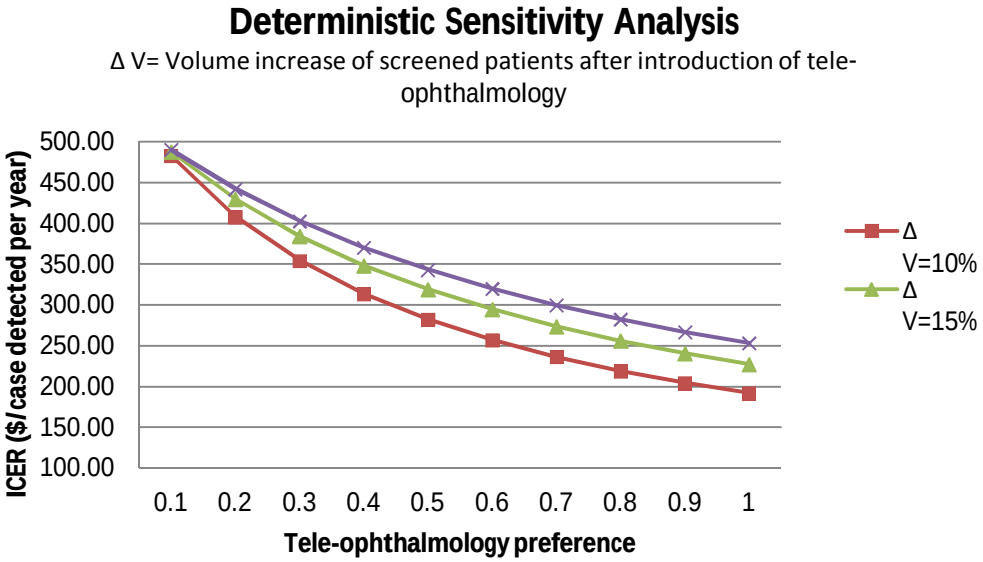

Figure 4.3 Two way sensitivity analysis. Influence of tele-ophthalmology preference and increased patience compliance after introduction of tele-ophthalmology on the incremental cost-effectiveness ratio (ICER)

Table 4.6 One-way deterministic sensitivity analysis results

Parameter	Base-case value	Range	ICER ($/case detected per year)
Prevalence of any diabetic retinopathy	0.225	0.169 to 0.281	$ 394.4 to $ 265.89
Patient preference for pharmacy-based tele-ophthalmology	0.40	0.40 to 0.70	$ 314.15 to $ 236.56
Diagnostic accuracy in-person examination			
Sensitivity	0.75	0.67 to 0.83	$ 282.0 to $ 361.2
Specificity	0.82	0.79 to 0.86	$ 287.0 to $ 350.2
Diagnostic accuracy tele-ophthalmology			
Sensitivity	0.84	0.76 to 0.91	$ 405.9 to $ 304.9
Specificity	0.94	0.90 to 0.97	$ 350.9 to $ 286.6
Proportion of dilated examinations (tele-ophthalmology)	0.337	0.25 to 0.47	$ 333.9 to $ 321.5
Rate of unreadable images (tele-ophthalmology)			
With pupil dilation	0.054	0.033 to 0.076	$ 306.6 to $ 321.5
Without pupil dilation	0.287	0.139 to 0.435	$ 209.9 to $ 411.2
Grader fee per patient (tele-ophthalmology)	$31.66	$ 23.75 to $ 55.41	$ 207.6 to $ 633.9
Tele-ophthalmology coordinator fee per patient	$4.03	$3.02 to $5.04	$300 to $327.8
Ophthalmic photographer	$6.05	$4.54 to $7.56	$300.05 to $327.8
In-person consultation	$51.10	$ 38.33 to $ 89.43	Tele-ophthalmology dominates at $ 77
Referral to retina specialist	$111.31	$ 83.48 to $ 139.14	$ 252.5 to $ 375.8

Chapter 5 Integrated discussion

5.1 Overview

This chapter outlines the thesis results and implications, and when appropriate it expands on the methodology used and interpretation of results. In summary, the purpose of this thesis was twofold: To assess the diagnostic accuracy of tele-ophthalmology for DR screening, and incorporate these findings in an economic model to explore the cost-effectiveness of a pharmacy-based tele-ophthalmology program in a semi-urban area.

5.2 Integrated discussion of thesis results

Chapter 3 of this thesis examined the diagnostic accuracy of tele-ophthalmology strategies for DR screening in adults as compared to reference standards. We conducted a systematic review in multiple databases from 1998 to 2012 (last update March 2013), and performed a meta-analysis categorizing results according to diagnostic threshold reported.

Results suggested that tele-ophthalmology programs fulfilled the minimum effectiveness requirements advised by the Canadian Ophthalmological Society (sensitivity over 80%, specificity between 90% and 95%).[1] For the detection of referable DR, we observed that the use of a single field per eye had a negative influence in the diagnostic performance of tele-ophthalmology programs, whereas the use of multiple photographic fields improved both sensitivity and specificity. For the detection of early DR forms, we found that the choice of reference standard affected the study results, in that studies that used 7-field fundus photographs (as advised by the American Telemedicine Association[2]) showed better sensitivity compared to studies that selected ophthalmologic examination as the reference. This is supported by previous evidence that shows that inaccurate reference standards underestimate the diagnostic accuracy of a test, being sensitivity more affected than specificity estimates.[3,4] We also observed that diagnostic performance for the detection of any DR improved over time. This is likely attributed to advances of digital camera technologies and data transmission

techniques, as a better resolution facilitates the identification of earlier signs of DR, reducing the number of false negatives.[5]

In Chapter 04, we explored the cost-effectiveness of pharmacy-based tele-ophthalmology for diabetic retinopathy screening in semi-urban Southwestern Ontario. Given that summary accuracy estimates were calculated for the detection of both any DR and referable retinopathy, we decided to address the cost-effectiveness of a category 1 tele-ophthalmology program, corresponding to the detection of any DR.[2] These estimates were more suitable for the economic model than the results of referable DR, since the definition of "any DR" was consistent amongst studies (ETDRS ≥20). Also, the summary prevalence was less variable across these studies compared to studies that used referable retinopathy as screening threshold, and resembled that of the Chatham-Kent population. Similarly, we used the meta-analysis information to calculate the weighted average of unreadable images according to use of pharmacologic dilation and incorporated these values into the economic model.

We found that pharmacy-based tele-ophthalmology was more costly, but more effective than in-person examination, at $478.3 per case detected and an incremental cost-effectiveness of $314.15 per additional case detected. Sensitivity analyses showed that unreadable images and physician's fees (for both in-person examination and tele-ophthalmology) influenced cost-effectiveness outcomes. In our model we discarded the assumption of exclusive initial use of tele-ophthalmology, as this situation would be highly unlikely in a semi-urban area where eye care specialists are permanently available. However, if we consider this assumption, the incremental cost-effectiveness decreases to $73.23 per additional case detected.

5.3 Thesis limitations and knowledge gaps in current literature

Meta-analyses of diagnostic test accuracy studies are particularly challenging as they usually incorporate primary studies that differ in study design, levels of quality and definition of test positivity.[6] Hence, greater variability is expected amongst diagnostic

accuracy studies versus clinical trial studies.[7] As commented in chapter 03, we detected substantial heterogeneity across studies, explored by means of subgroup analyses. Amongst studies that detected any DR (category 1), heterogeneity was partially explained by the differential use of reference standard and pharmacologic dilation. Variability of the summary sensitivity was significantly reduced when low quality studies were excluded from the analysis (Base-case I^2=90; Q=154 vs. I^2=31; Q=8.8) , reflecting the influence of study design deficiencies on accuracy estimates. Hence, methodological differences in study design, data collection and reporting of diagnostic accuracy estimates may account for part of heterogeneity observed in the meta-analysis results (methodological bias).[8,9]

In contrast to our findings amongst category 1 studies (detection of any DR), considerable heterogeneity remained unexplained even after subgroup and sensitivity analyses on studies that detected referable DR (category 2). In this case, heterogeneity could be partially explained by a threshold effect, since authors in this category used diverse guidelines (or even personal criteria) to define test positivity. There may be other significant sources of heterogeneity that we could not address in our analysis due to the small number of primary studies within subgroups, or lack of adequate reporting in primary studies (discussed below).

Variability due to clinical characteristics was not addressed in this thesis, as this information was poorly reported in primary studies. For instance, only 50% of studies presented information about ethnicity, type of diabetes and duration of diabetes. Lack of clinical and demographic information limits the interpretation of the actual usefulness of tele-ophthalmology screening program. This also impacts the interpretability of the economic analysis findings; it could be possible that some patient subgroups may have greater benefit from a pharmacy-based tele-screening program. In addition to the lack of reporting of clinical characteristics, index technology details such as camera resolution, image compression, screen display size and resolution were not described in most studies, restricting the assessment of the potential effect of these

technological features on the diagnostic performance of screening programs in the public health setting. However, we were able to evaluate the influence of number of photographic fields per eye and pharmacologic dilation on the diagnostic performance of tele-ophthalmology programs, which have been subject of intense debate amongst experts regarding their relevance on the diagnostic yield of this procedure.[10,11]

Although methodological quality of primary studies was satisfactory, we detected a high risk of patient selection bias and risk of bias due to exclusion of patients with uninterpretable test results. Most of excluded patients presented comorbidities (e.g cataracts) that restricted image interpretation. An inadequate selection of patients, as in this case, may lead to an overestimation of sensitivity and specificity.[12] Even though this is considered a source of bias by some authors, evidence regarding the effect of exclusion of patients due to uninterpretable results is very limited, and a definitive association with inflated diagnostic accuracy estimates has not been demonstrated.[13]

In the economic analysis, we chose the detection of any DR as the threshold for test positivity, which by definition corresponds to a Category 1 telehealth program.[2] The main objective of this program is to increase adherence to screening standards amongst diabetic patients, and serve as a platform for surveillance and education of those individuals at risk of developing DR. However, direct management and treatment of potential cases of severe vision loss correspond to more complex telemedicine programs that use additional features such as stereopsis that permit an accurate categorization of DR severity levels, including detection of diabetic macular edema.[14] Hence, the interpretation of the cost-effectiveness estimates is limited to the incremental cost per additional case detected and the incremental cost per case correctly diagnosed.

Although macular edema is a very important complication from DR, tele-ophthalmology programs without stereopsis (e.g Category 1 and 2 telehealth programs) are technically limited to assess this condition.[2] However, several studies have found that early clinical signs of DR detected in tele-ophthalmology examinations may act as proxy indicators for

clinically significant macular edema.[15,16] From the meta-analysis, we examined primary studies that reported diagnosis of macular edema, and found that 32 out of 33 cases were detected along with DR cases.[17–19] Hence, a combination of digital photography and visual acuity estimation may be useful to evaluate the presence of clinically significant macular edema in a category 1 telehealth program. Validation studies must be conducted to explore this alternative.

5.4 Conclusions and future directions

Our study indicated that diagnostic performance of tele-ophthalmology programs is satisfactory and fulfills Canadian Ophthalmological Society's criteria for DR screening (sensitivity >80%, specificity between 90% and 95%)[1]. However, the clinical significance of these findings is somewhat inconclusive due to the presence of significant heterogeneity, which remained partially unexplained after subgroup and sensitivity analyses. Hence, careful judgment should be exercised when interpreting the applicability of these summary estimates in clinical practice.

Of note, we found lack of reporting of important clinical characteristics and technology features, which in turn limited the assessment of these variables in the meta-analysis. This is an issue of paramount importance that should be addressed by investigators and journal editors, as an adequate reporting of these features will warrant a comprehensive examination of sources of variation in future reviews.[20]

Although the diagnostic performance of tele-ophthalmology was satisfactory, the cost-effectiveness of a pharmacy-based tele-ophthalmology program in a semi-urban population is unclear. While this program was more effective than in-person examination, an additional cost of $314.1 per case detected may be too high from the healthcare payer perspective. Hence, this economic analysis opens the discussion as if the benefits of mobile tele-ophthalmology in semi-urban areas are equivalent to those benefits observed in remote populations. Prospective studies will provide more insight on the impact of such programs on prevention of severe vision loss and quality of life in a semi-urban setting.

5.5 References

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Appendix

Appendix A. Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist

Reporting background should include	**Page**
Problem definition	48
Hypothesis statement	48
Description	48
Type of exposure or intervention used	48, 49
Type of study designs used	49
Study population	49
Reporting of search strategy should include	
Qualifications of searches (e.g. librarians and investigators)	49, 50
Search strategy, including time period included in the synthesis and keywords	48, Appendix C
Effort to include all available studies, including contact with authors	49,50
Databases and registries searched	48
Search software used, name and version, including special features	49
Use of hand searching (e.g. reference lists of obtained articles)	49
List of citations located and those excluded including justification	72
Method of addressing articles published in languages other than English	50
Method of handling abstracts and unpublished studies	-
Description of any contact with authors	54
Reporting methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	50
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	50
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	49,50
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	51
Assessment of heterogeneity	52,53
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	51, 52
Provision of appropriate tables and graphics	72-81
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	78, 79
Table giving descriptive information for each study included	73
Results of sensitivity testing (eg, subgroup analysis)	81
Indication of statistical uncertainty of findings	61
Reporting of discussion should include	

Quantitative assessment of bias (eg, publication bias)	53
Justification for exclusion (eg, exclusion of non–English-language citations)	54
Assessment of quality of included studies	55
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	60, 61
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	61
Guidelines for future research	61
Disclosure of funding source	54

Appendix B. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist

Section/topic	#	*Checklist item*	*Reported on page #*
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	46
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	48
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	48
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	49
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	48, 49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	App. C
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	49
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	49, 50

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	50
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	53
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	52
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	52, 53
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	53, 54
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	53
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	72
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	73
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	77, 78, 83
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	78, 79
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	79
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	77, 78
Additional	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see	81, 82

analysis		Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	59
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	60
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	61
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	54

Appendix C Complete search strategies for primary databases

C.1. Medline search strategy (OVID)

#	**Search terms**
1	Diabetic Retinopathy/ or macular edema/ or fundus oculi/
2	(diabetic retinopath$ or diabetic maculopath$ or macular edema or macular oedema or fovea edema or fovea oedema or fundus oculi).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3	(fundus adj10 (eye or retina$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4	1 or 2 or 3
5	exp Diagnosis/ or diagnostic imaging/
6	diagnos$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7	5 or 6
8	telemedicine/ or telepathology/ or photography/ or vision screening/
9	(telescreen$ or automated screen$ or digital imag$ or tele-screen$ or teleophthalmology or tele-ophthalmology or digital screen$ or photograph$ or vision screen$ or image anal$ or telemedicine or telepathology or teleconsult$ or tele-consult$ or telehealth).mp.
10	8 or 9
11	exp "Sensitivity and Specificity"/ or comparative effectiveness research/ or exp evaluation studies as topic/
12	(sensitiv$ and specificit$).mp.
13	evaluation studies.pt.
14	evaluation stud$.mp.
15	11 or 12 or 13 or 14
16	1 and 7 and 10 and 15
17	Limit 16 to yr=”1998-Current”

C.2. EMBASE search strategy (OVID)

#	**Search terms**
1	Diabetic Retinopathy/ or retina macula edema/ or eye fundus/
2	(diabetic retinopath$ or diabetic maculopath$ or macular edema or macular oedema or macula edema or macula oedema or fovea edema or fovea oedema or fundus oculi).mp.
3	(fundus adj5 (eye or retina$)).mp.
4	1 or 2 or 3
5	exp Diagnosis/ or diagnostic imaging/
6	diagnos$.mp.
7	5 or 6

8	telemedicine/ or teleconsultation/ or telehealth/ or telepathology/ or exp medical photography/ or image analysis/ or vision test/
9	(telescreen$ or automated screen$ or digital imag$ or tele-screen$ or telehealth or teleconsult$ or tele-consult$ or teleophthalmology or tele-ophthalmology or digital screen$ or medical photograph$ or vision screen$ or image anal$ or telemedicine or telepathology).mp.
10	8 or 9
11	"Sensitivity and Specificity"/ or Comparative Studies/ or Comparative Effectiveness/ or Evaluation/
12	(sensitiv$ and specificit$).mp.
13	(Comparative stud$ or comparative effectiveness or evaluat$).mp.
14	11 or 12 or 13
15	4 and 7 and 10 and 14
16	limit 20 to yr="1998 -Current"

C.3. BIOSIS search strategy (Web of Knowledge)

#	**Search terms**
#1	“diabetic retinopath*” or ”diabetic maculopath*” or “macular edema” or “macular oedema” or “fovea edema” or “fovea oedema” or “fundus oculi”
#2	fundus same (eye or retina*)
#3	#1 or #2
#4	Concept Codes=(Pathology - Diagnostic) OR Topic=(diagnos*)
#5	Concept Codes=(Methods - Photography OR Public health - Health services "and" medical care)
#6	telescreen* or “automated screen*” or “digital imag*” or tele-screen* or teleophthalmology or tele-ophthalmology or “digital screen*” or photograph* or “vision screen*” or “image anal*” or telemedicine or telehealth or telepathology or teleconsult* or ”tele-consult*”
#7	#5 or #6
#8	“comparative stud*" or "evaluation research" or "evaluation stud*" or "comparative effectiveness" or (sensitiv* SAME specific*)
#9	#8 AND #7 AND #4 AND #3 Timespan=1998-2012. Databases=BIOSIS Previews. Lemmatization=On

C.4. Web of Science search strategy (Web of knowledge)

#	**Search terms**
#1	“diabetic retinopath*” or ”diabetic maculopath*” or “macular edema” or “macular oedema” or “fovea edema” or “fovea oedema” or “fundus oculi”
#2	fundus same (eye or retina*)

#3	#1 or #2
#4	diagnos*
#5	telehealth or teleconsult* or “tele-consult*” or telescreen* or "automated screen*" or "digital imag*" or “tele-screen*” or teleophthalmology or tele-ophthalmology or "digital screen*" or photograph* or "vision screen*" or "image anal*" or telemedicine or telepathology
#6	“comparative stud*" or "evaluation research" or "evaluation stud*" or "comparative effectiveness" or (sensitiv* SAME specific*)
#7	#6 AND #5 AND #4 AND #3

C.5. Cochrane library search strategy (Wiley online library)

#	**Search terms**
#1	MeSH descriptor Diabetic Retinopathy, this term only
#2	MeSH descriptor Macular Edema, this term only
#3	MeSH descriptor Fundus Oculi, this term only
#4	“diabetic retinopathy” or “diabetic retinopathies” or “diabetic maculopathy” or “diabetic maculopathies” or macular edema or macular oedema or fovea edema or fovea oedema or fundus oculi NEED “ “ around all phrases, eg “fovea edema”
#5	Fundus NEAR/5 (eye OR retina*)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor Diagnosis explode all trees
#8	MeSH descriptor Diagnostic Imaging, this term only
#9	diagnos*
#10	#7 or #8 or #9
#11	MeSH descriptor Telemedicine, this term only
#12	MeSH descriptor Telepathology, this term only
#13	MeSH descriptor Photography, this term only
#14	MeSH descriptor Vision screening, this term only
#15	telemedicine or telehealth or teleconsult or teleconsultation or "tele-consult" or "tele-consultation" or telescreen or telescreening or "automated screen" or "automated screening" or "digital images" or "digital imaging" or "digital image" or "tele-screen" or "tele-screening" or teleophthalmology or "tele-ophthalmology" or "digital screen" or "digital screening" or photography or photographic or "vision screening" or "vision screen" or "image analysis" or telepathology
#16	#11 or #12 or #13 or #14 or #15
#17	MeSH descriptor Sensitivity and Specificity explode all trees
#18	MeSH descriptor Comparative Effectiveness Research, this term only
#19	MeSH descriptor Evaluation Studies as Topic explode all trees
#20	(evaluation studies):pt
#21	(sensitiv* and specificit*) or "comparative effectiveness" OR "evaluation

	study" or "evaluation studies" or evaluat*
#22	#17 OR #18 OR #19 OR #20 OR #21
#23	#6 and #10 and #16 and #22 from 1998 to 2012

C.6. CINAHL Search strategy (EBSCO host)

#	**Search terms**
S1	MH "Diabetic Retinopathy"
S2	diabetic retinopath* or diabetic maculopath* or macular edema or macular oedema or fovea edema or fovea oedema or fundus oculi NEED " " around all phrases, eg "macular edema"
S3	fundus N10 (eye or retina*)
S4	S1 or S2 or S3
S5	MH "Diagnosis" OR MH "Diagnosis, Eye+" OR MH "Diagnostic Imaging"
S6	Diagnos*
S7	S5 or S6
S8	MH "Telehealth" OR MH "Telemedicine" OR MH "Remote Consultation" OR MH "Telepathology" OR MH "Photography" OR MH "Digital Imaging" OR MH "Vision Screening"
S9	telescreen* or automated screen* or digital imag* or tele-screen* or teleophthalmology or tele-ophthalmology or digital screen* or photograph* or vision screen* or image anal* or telehealth or telepathology or telemedicine or teleconsult* or "tele-consult*" or "remote consult*" NEED " " around all phrases, eg "automated screen*"
S10	S8 or S9
S11	MH "Sensitivity and Specificity" OR MH "Comparative Studies" OR MH "Evaluation Research" OR MH "Summative Evaluation Research"
S12	sensitiv* and specificit*
S13	evaluation stud* NEED " " around all phrases,
S14	S11 or S12 or S13
S15	S4 and S7 and S10 and S14
S16	S4 and S7 and S10 and S14 Limiters - Published Date from: 19980101-20121231

Appendix D. Data collection form

Diagnostic accuracy of tele-ophthalmology for diabetic retinopathy screening

1. Study features

a) Citation (author, year)

b) Country

c) Language

d) Study objective

e) Funding source

2. Sample characteristics

a) Patient recruitment

b) Inclusion/exclusion criteria

c) Number of patients approached

d) Number of patients fully screened

e) Demographics

	Yes	No	Not reported	Mean (SD) OR Median (range) OR proportion			
Age							
Race/ethnicity				Caucasian	African-American	Hispanic	Other
Type I diabetes							
Type II diabetes							
Visual acuity							
Any diabetic retinopathy prevalence							
Referable diabetic retinopathy prevalence							
Patient diagnosis							
Definition of referable diabetic retinopathy (if applicable)							

f) Unit of study

- [ ] Eye
- [ ] Patient
- [ ] Not reported

3. Screening details

a) Reference standard used

- [ ] 7-field ETDRS photographs
- [ ] Slit-lamp biomicroscopy
- [ ] Not reported

b) Grading guideline used

- [ ] Modified Airlie House Classification
- [ ] European Field Guide
- [ ] International Clinical Diabetic Retinopathy Scale
- [ ] Other (please specify)
- [ ] Not reported

c) Index technology

i. Fundus camera

Camera brand	
Camera resolution	

ii. Image acquisition (be as specific as possible)

Technician:

- [ ] Certified photographer
- [ ] Nurse
- [ ] Eye care professional
- [ ] Other (please specify)
- [ ] Not reported

Number of fields taken per eye:

- [ ] One
- [ ] Two
- [ ] Three

Four	
Five	
More than five	
Not reported	

Field positioning:

Stereopsis

Yes	
No	
Not reported	

Pupil dilation

Yes/mixed	
No	
Not reported	

Mydriatic agent (if applicable):

iii. Image quality

	Yes	No	Not reported	Proportion OR compression ratio
Unreadable images (%)				
Image compression				

4. Diagnostic accuracy

	Sensitivity (95% CI)	Specificity (95% CI)	TP	FN	FP	TN
Any Diabetic Retinopathy						
Referable Diabetic Retinopathy						

5. Additional comments of the reviewer

Appendix E. Adapted QUADAS2 criteria

Phase 1: **State the review question**
Author:
Index test(s):
Reference standard:
Unit of study:
Phase 2: **Draw a flow diagram for the primary study**

Phase 3: **Risk of bias judgments**

DOMAIN 1: Patient selection

a. Describe methods of patient selection:

b. Signaling questions

Grading: If at least one "No", then Risk of bias is HIGH. If at least one "Unclear", then Risk of bias is "UNCLEAR".

1) *Was a consecutive or random sample of patients enrolled?*

Yes	☐
No	☐
Unclear	☐

2) *Did the study avoid inappropriate exclusions?*

Yes	☐
No	☐
Unclear	☐

Could the selection of patients have introduced bias?
RISK:

HIGH	☐
LOW	☐
UNCLEAR	☐

DOMAIN 2: Index test(s)
Please complete for each index test

a. Describe the index test and how it was conducted and interpreted:

b. Signalling questions

Grading: If at least one "No", then Risk of bias is HIGH. If at least one "Unclear", then Risk of bias is "UNCLEAR".

3) *Were the index test results interpreted without knowledge of the results of the reference standard?*

Yes	☐
No	☐
Unclear	☐

4) *If a threshold was used, was it pre-specified?*

Yes	☐
No	☐
Unclear	☐

Could the conduct or interpretation of the index test have introduced bias?
RISK:

HIGH	☐
LOW	☐
UNCLEAR	☐

DOMAIN 3: Reference standard

a. Describe the reference standard and how it was conducted and interpreted:

b. Signalling questions

Grading: If at least one "No", then Risk of bias is HIGH. If at least one "Unclear", then Risk of bias is "UNCLEAR".

5) *Is the reference standard likely to correctly classify the target condition?*

Yes	☐
No	☐
Unclear	☐

6) *Were the reference standard results interpreted without knowledge of the results of the index test?*

Yes	☐
No	☐
Unclear	☐

Could the reference standard, its conduct, or its interpretation have introduced bias?
RISK:

HIGH	☐
LOW	☐
UNCLEAR	☐

DOMAIN 4: Flow and timing

a. Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram)

b. Describe the time interval or any interventions between index test(s) and the reference standard

c. Signaling questions

Grading: If at least one "No", then Risk of bias is HIGH. If at least one "Unclear", then Risk of bias is "UNCLEAR".

7) *Was there an appropriate interval link between index test(s) and reference standard?*

Yes	☐
No	☐
Unclear	☐

8) *Did all patients receive the same reference standards?*

Yes	☐
No	☐
Unclear	☐

9) *Were all patients included in the analysis?*

Yes	☐
No	☐
Unclear	☐

Could the patient flow have introduced bias?
RISK: HIGH/LOW/UNCLEAR

HIGH	☐
LOW	☐
UNCLEAR	☐

Appendix F. Paired forest plots – Sensitivity analyses of included studies per category (category 1, detection of any diabetic retinopathy; category 2, detection of referable diabetic retinopathy)

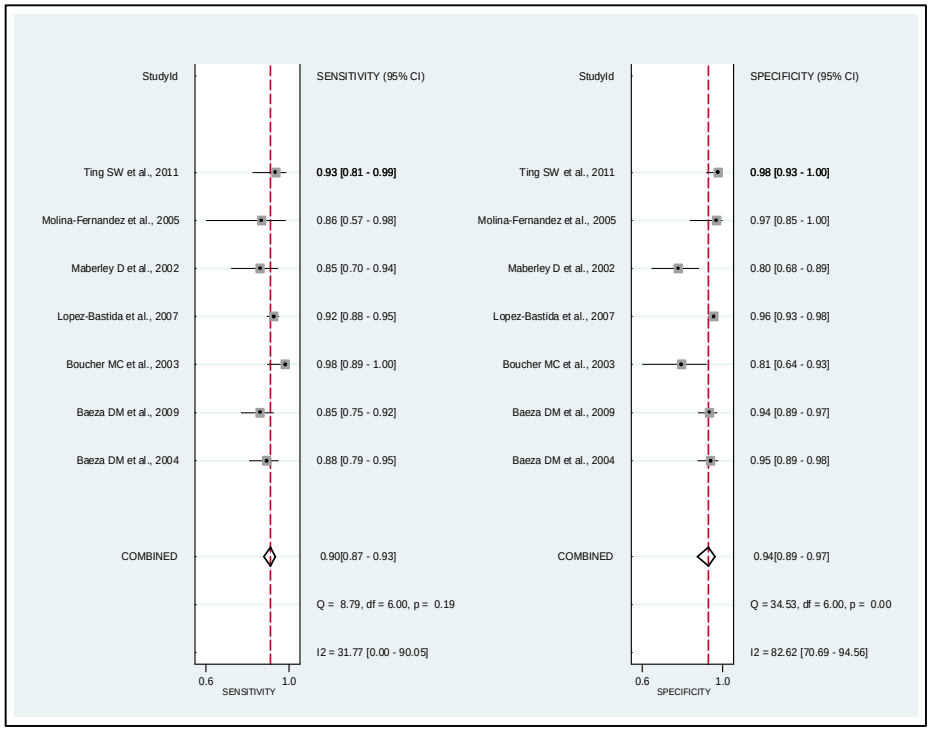


Figure 1a Category 1 studies – sensitivity analysis excluding studies with high/uncertain risk of bias as graded by QUADAS2 criteria

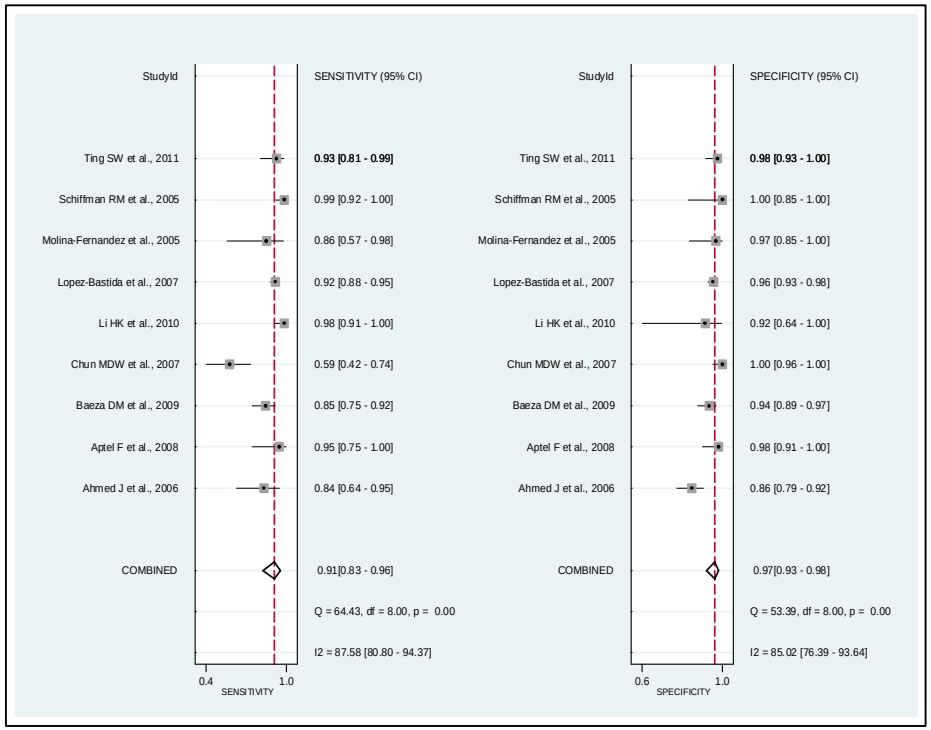


Figure 1b Category 1 studies – sensitivity analysis excluding studies published prior 2005

Appendix F. (Continued)

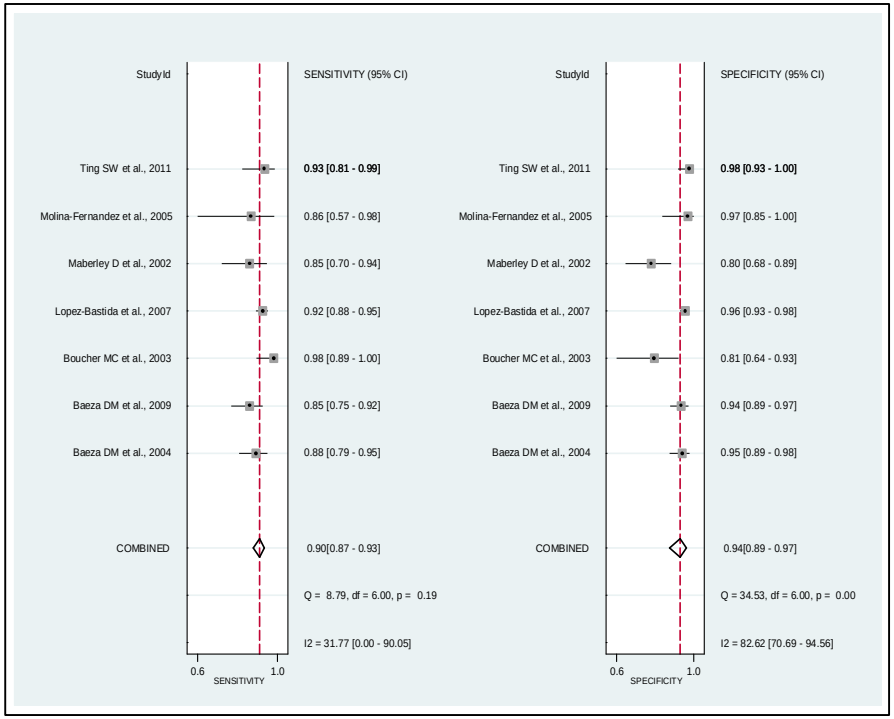


Figure 2a Category 2 studies – sensitivity analysis excluding studies with high/uncertain risk of bias as graded by QUADAS2 criteria

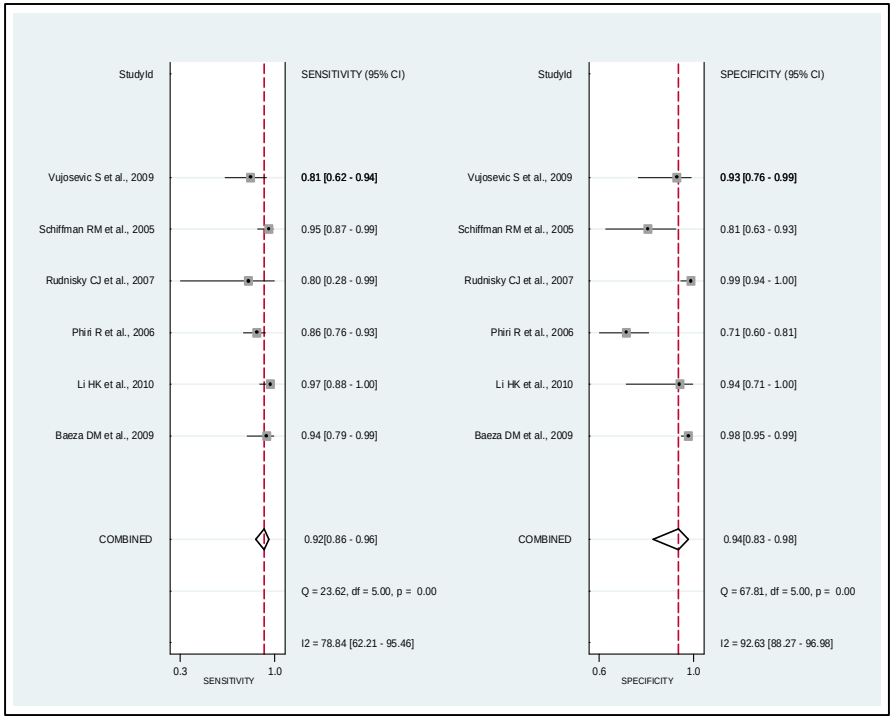
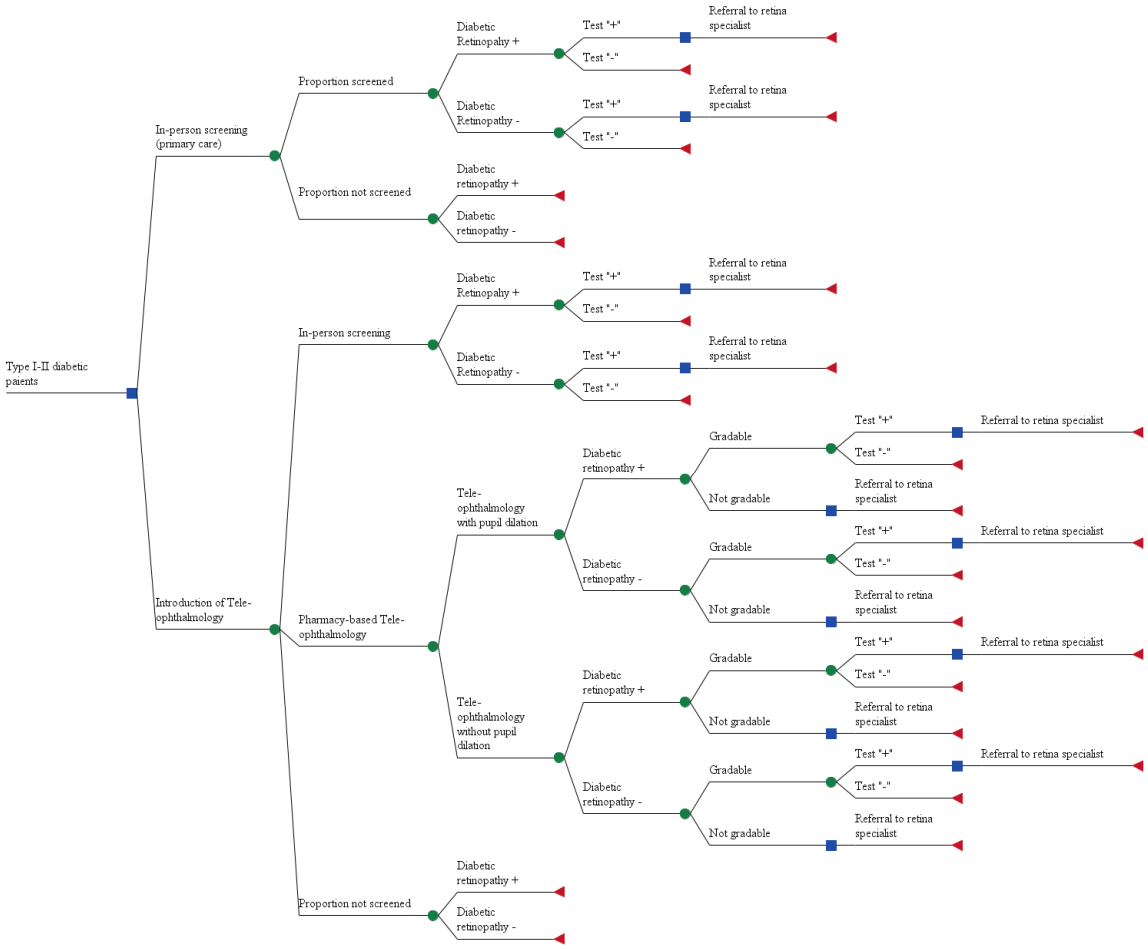


Figure 2b Category 2 studies – sensitivity analysis excluding studies published prior 2005

Appendix G. Decision tree model for tele-ophthalmology versus in person examination



Appendix H. Search strategy (Pubmed and EMBASE). Compliance after introduction of mobile units for eye assessment and patient preferences for screening with mobile units

H.1 Medline

	Search terms
1	*Telemedicine/ or exp Mobile Health Units/ or exp Community Pharmacy Services/
2	(tele-medicine or tele-screening or telescreening or mobile health unit$ or community pharmac$ service$).mp.
3	1 or 2
4	Eye diseases/ or Ophthalmology/ or Retinal Diseases/ or Retina/pa or exp Diabetic Retinopathy/
5	(eye disease$ or retinal disease$ or retina$ or diabetic retinopath$).mp.
6	4 or 5
7	Mass Screening/ or diagnosis/ or early diagnosis/
8	3 and 6 and 7

H.2 Embase

	Search terms
1	telediagnosis/ or telemedicine/ or preventive health service/
2	(telediagnos$ or telemedicine or tele-medicine or telescreening or tele-screening or preventive health service$).mp.
3	1 or 2
4	eye disease/ or retina disease/ or diabetic retinopathy/
5	(eye disease$ or retina disease$ or retina$ or diabetic retinopath$).mp.
6	4 or 5
7	diagnosis/ or early diagnosis/ or exp mass screening/
8	3 and 6 and 7

Appendix I. Calculation of model probabilities

I.1 Calculation of screening probabilities for in-person examination (Arm 1) and tele-ophthalmology (Arm 2)

I.1.1 In-person examination (Arm 1)

$P_{(ref)}$= 0.511 Ontario examination rate of diabetic patients one year after receiving a diabetes diagnosis (Buhrmann *et al.,* 2003)

Proportion of non-compliant patients is defined as 1- $P_{(ref)}$ = 0.489

I.1.2 Tele-ophthalmology screening (Arm 2)

From the literature search (Appendix H) it is assumed a 10% volume increase (V) of screening examinations after introduction of mobile retinal screening (Olayiwola JN *et al.*, 2011).

We have the following screening rate after introduction of tele-ophthalmology

$$P_{(Arm\ 2)} = P_{(ref)} \times V$$

Where,

V= Volume increase of screening examinations after introduction of mobile retinal screening.

$P_{(Arm\ 2)}$= 0.511 x 1.10= 0.5621

I.1.2.1 Proportion of tele-ophthalmology examinations within Arm 2

To calculate the proportion of examinations with tele-ophthalmology within Arm 2 we have the following

$$P_{(tele)} = T\ (P_{(ref)} \times V)\ ,\ V \geq 1,\ P_{(tele)} < 1$$

Where,

T= Proportion of patients that accept a tele-ophthalmology examination

From the literature search (Appendix H) we assumed that 40% of screened patients accepted a tele-ophthalmology examination (T), and the remaining 60% preferred the in-person examination.

$P_{(tele)}$= 0.40 (0.5621)= 0.2248

I.1.2.2 Proportion of in-person examinations within Arm 2

The proportion of in-person examinations ($P_{(inp)}$) is defined as

$P_{(inp)}= P_{(Arm\ 2)} - P_{(tele)}$

$P_{(inp)}$= 0.3373

I.1.2.3 Proportion of non-compliant patients

Proportion of non-compliant patients is defined as

$P_{(nc)}= 1- P_{(Arm2)}$

$P_{(nc)}$= 0.4379

Appendix J. Summary of probabilities incorporated in the economic model

Notation	Details	Value
Base tree		
p	Patients screened with current practice (Arm 1)	0.511
1-p	Patients not screened (Arm 1)	0.489
q	Patients would prefer in-person examination over tele-ophthalmology	0.60
1-q	Patients would prefer tele-ophthalmology	0.40
p(n)	Patients screened after implementation of tele-ophthalmology (Arm 2)	0.5621
[p(n)]*[q]	Patients screened with in-person examination (Arm 2)	0.3373
[p(n)]*[1-q]	Patients screened with tele-ophthalmology (Arm 2)	0.2248
1-[(6)+(7)]	Patients not screened (after tele-ophthalmology)	0.4379
In-person examination		
se_primary	Test "+" (among diseased)	0.75
1-[se_primary]	Test "-" (among diseased)	0.25
sp_primary	Test "-" (among non-diseased)	0.82
1-[sp_primary]	Test "+" (among non-diseased)	0.18
Tele-ophthalmology		
d	Patients with dilated examination	0.337
1-d	Patients with undilated examination	0.663
u_d	Unreadable images with pupil dilation	0.0547
1-[u_d]	Readable images with pupil dilation	0.9453
u_nod	Unreadable images without dilation	0.2874
1-[u_nod]	Readable images without dilation	0.7126
se_tele	Test "+" (among diseased)	0.89
1-[se_tele]	Test "-" (among diseased)	0.11
sp_tele	Test "-" (among non-diseased)	0.94
1-[sp_tele]	Test "+" (among non-diseased)	0.06
DR_yes	Proportion with any DR (prevalence)	0.225
1-[DR_yes]	Not diseased	0.775

Appendix K. Search strategy (Medline, Embase)

K.1 Medline

#	Search terms
1	Diabetic Retinopathy/ or macular edema/ or fundus oculi/
2	(diabetic retinopath$ or diabetic maculopath$ or macular edema or macular oedema or fovea edema or fovea oedema or fundus oculi).mp.
3	1 or 2
4	exp Diagnosis/ or diagnostic imaging/
5	(diagnos$ or screen$).mp.
6	4 or 5
7	"costs and cost analysis"/ or "cost allocation"/ or cost-benefit analysis/ or exp "cost control"/ or health care costs/ or direct service costs/ or employer health costs/ or hospital costs/ or exp health expenditures/ or Decision Trees/ or markov chains/
8	(cost-effective$ or cost effective$ or cost-benefit or cost benefit or decision tree$ or markov model$ or economic analys$).mp.
9	7 or 8
10	3 and 6 and 9
11	Diabetic Retinopathy/ec [Economics]
12	**10 or 11**

K.2 Embase

#	Search terms
1	Diabetic Retinopathy/ or retina macula edema/ or eye fundus/
2	(diabetic retinopath$ or diabetic maculopath$ or macular edema or macular oedema or macula edema or macula oedema or fovea edema or fovea oedema or fundus oculi).mp.
3	1 or 2
4	exp Diagnosis/ or diagnostic imaging/
5	diagnos$.mp.
6	4 or 5

7	*"cost effectiveness analysis"/
8	economic evaluation/ or health care cost/ or decision tree/
9	7 or 8
10	(cost-effective$ or cost effective$ or decision tree$ or economic analys$).mp.
11	9 or 10
12	**3 and 6 and 11**

Curriculum Vitae

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Ontario Graduate Scholarship (OGS)
Ministry of Training, Colleges and Universities
2012-2013

Schulich Graduate Scholarship
Western University
2011-2013

Peer Reviewed Abstracts:

"Effectiveness of Telemedicine Strategies for Diabetic Retinopathy Diagnosis: A Systematic Review".
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Seattle, Washington State (US). May 5th-9th, 2013 **Presenter**

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Canadian Society of Epidemiology and Biostatistics (CSEB) Biennial Conference. St. John's, Newfoundland (Canada). June 25th-27th, 2013 **Presenter**