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00212 Eye Research

**Telemedicine and non-mydriatic digital retinal imaging
in the detection of ocular pathology other than
diabetic retinopathy in patients with diabetes:**

A comparison with dilated clinical eye examination and
mydriatic seven-standard field fundus photography

A research thesis by
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STUDENT DECLARATION

All material presented in this thesis is my original work unless otherwise specified. No other person's work has been used without due acknowledgement. I have received direction and feedback in writing this thesis from A/Professor Lloyd Paul Aiello, A/Professor Jill Keeffe and Dr. Alex Harper. I have obtained statistical advice from Allen Clermont. Digital retinal images from the Joslin Vision Network (JVN) platform were acquired by the JVN clinical team at the Joslin Diabetes Institute (Boston, USA). Digital retinal images and mydriatic fundus photographs from the Centre for Eye Research Australia (Melbourne, Australia) were provided by Dr. Reuben Phiri.

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ABSTRACT

Background and Purpose: The Joslin Vision Network (JVN) telemedicine initiative of the Joslin Diabetes Center in Boston, USA aims to facilitate access for patients with diabetes currently receiving sub-optimal or no eye care into chronic disease management within the Joslin Diabetes Eye Health Care Model. Prior studies validated non-mydriatic digital imaging with the JVN for detecting specific clinical levels of diabetic retinopathy (DR) compared with the gold-standard of stereoscopic Early Treatment Diabetic Retinopathy Study (ETDRS) mydriatic seven standard field 35-mm slide fundus photographs¹ and clinical examination by retinal specialist ophthalmologists via dilated fundus examination.²

This study aims to evaluate the ability of non-mydriatic digital imaging with the JVN to detect common ocular disorders other than DR in patients with diabetes by comparison to a dilated clinical eye examination by retinal specialist ophthalmologists. Part two of this study will further examine the ability of non-mydriatic digital retinal imaging to detect non-diabetes-related (non-DR) ocular findings in a cohort of diabetic patients in Melbourne, Australia as compared with ETDRS fundus photographs.

Methods: 952 patients with diabetes new to the Joslin Diabetes Center's outpatient clinic underwent non-mydriatic digital retinal imaging with the JVN as per JVN protocol³ between 1st January and 31st July, 2003. Of these, 280 patients (29.4%) subsequently had a dilated clinical examination by a retinal specialist. Retrospective chart review compared findings from all 280 patients' medical records with findings from their JVN Evaluation Report. Disagreements were adjudicated by an independent masked senior retinal specialist through review of ETDRS photographs when available and JVN images.

In Melbourne, 140 patients with diabetes presenting to the Primary Care and Retina clinics at the Royal Victorian Eye and Ear Hospital between 1st January and 31st July, 2003 underwent both non-mydratic digital imaging and mydratic ETDRS seven standard field photography. These digital images and photographs were subsequently graded by independent masked readers for non-DR ocular findings and compared.

Results: In the JVN patient cohort, average patient age at imaging was 50.0 ± 14.9 years. 43.5% were female, 69.2% had type 2 diabetes mellitus (DM), average DM duration was 10.6 ± 9.6 years and average interval between JVN and clinical examination was 39.6 days. Of 560 eyes from 280 patients, JVN images from 545 eyes (97.3%) were gradable for non-DR lesions. JVN identified at least one non-DR ocular finding in 114 patients (40.7%) including in 22.8% of eyes with no diabetic retinopathy (59/259). Non-DR lesions identified by eye via the JVN and/or clinical examination included retinal emboli (n=3), retinitis pigmentosa (n=1), asteroid hyalosis (n=1), chorio-retinal atrophy and/or scar (n=6), epiretinal membrane (n=11), choroidal lesions in order to rule out choroidal melanoma (n=18), evidence of a systemic factor such as hypertension or renal disease contributing to retinopathy (15 patients), retinal indicators for suspicion of glaucoma (18 patients), cataract (n=100) and age-related macular degeneration (AMD) and/or macular drusen (n=52). Agreement for either presence or absence of these findings within JVN fields was 100%, 100%, 100%, 100%, 99.6%, 98.6%, 98.2%, 98.2%, 95.4%, 91.3% respectively. Kappa values for most non-DR lesions within JVN fields demonstrated almost perfect agreement ($\kappa \geq 0.80$) with substantial agreement for AMD and macular drusen ($\kappa=0.71$) and choroidal lesions ($\kappa=0.73$).

In the Melbourne cohort, average patient age was 69.1 ± 9.9 years. 44.3% were female, 95.7% were diagnosed with DM ≥ 30 years of age and average DM duration was 12.6 ± 7.7 years. Both non-mydriatic digital images and ETDRS photographs were obtained on the same day. Of 279 eyes from 140 patients, digital images from 260 eyes (93.2%) were gradable for non-DR lesions. Digital images identified 76 patients (54.3%) with at least one non-DR finding. Non-DR lesions identified by eye via digital imaging and/or ETDRS photographs include macular hole (n=2), asteroid hyalosis (n=1), bilateral myopic degeneration of the disc (3 patients), chorio-retinal atrophy and/or scar (n=4), central and/or branch retinal vein occlusion (n=4), epiretinal membrane (n=3), choroidal lesions (n=7), suspicion of glaucoma (n=8), AMD and/or macular drusen (n=43) and cataract (n=52). Agreement for either presence or absence of these findings was 100%, 100%, 99.3%, 99.3%, 98.9%, 98.9%, 97.5%, 97.1%, 91.8% and 90.0% respectively. For most non-DR lesions, Kappa values assessing agreement demonstrated moderate to substantial agreement ($\kappa=0.40 - 0.79$) with almost perfect agreement ($\kappa=0.80$) for myopic degeneration of the disc.

Conclusion: Substantial to almost perfect agreement between JVN findings and dilated clinical examination suggests that the JVN system has the potential to provide eye evaluation for disorders other than DR. In addition, the large number of diabetic patients with non-DR findings and no diabetic retinopathy (22.8%) reinforces the importance of regular retinal evaluation even in patients without extensive retinopathy. Additional prospective studies are justified to validate the ability of the JVN to diagnose and manage non-DR ocular disorders.

Similarly promising results from the Melbourne cohort also suggests the potential of non-mydriatic digital retinal imaging as an adjunct to current eye evaluation modalities, particularly in view of its advantages to facilitate outreach into the community.

BACKGROUND AND PURPOSE

BACKGROUND

Methodology for literature review

Medline (January 1966 to May 2004), the Cochrane Library (Cochrane Database of Systematic Reviews; Cochrane Diabetes Group specialised register; Cochrane Central Register of Controlled Trials; Health Technology Assessment database) and the World Health Organisation (WHO) database were utilised for literature review. The words “digital imaging”, “retinal imaging”, “fundus imaging”, “fundus photography”, “digital photography”, “telemedicine”, “diabetes”, “diabetic retinopathy”, “screening” and “barriers” were entered as search terms, before being mapped to subject headings. The terms “diabetes *and...*” were also combined and entered with the latter term being the ocular finding of interest. (For example, diabetes *and* epiretinal membrane)

Diabetes and diabetic retinopathy: the magnitude of this public health concern

Diabetes mellitus is a complex chronic disease that requires continuing medical care and patient self-management education in order to minimize acute and long-term complications.ⁱ

Complications primarily involve cardiovascular, neurological, renal and ocular systems. Worldwide, diabetes currently affects 150 million people and its prevalence is predicted to escalate to 300 million in the next 25 years.ⁱⁱ In the United States of America (USA) and Australia, 17.7 million and 950,000 people respectively currently have diabetes, with figures estimated to exceed 30 million in the US and 1.6 million in Australia by 2030.ⁱⁱⁱ The prevalence of diabetes in both countries is comparable at 6.2% in the US^{iv} and 7.4% in Australia.^v

Diabetes also disproportionately affects minority groups in both the US and Australia. In the US, prevalence rates for diabetes among African-Americans (12.5%) and Mexican Americans (13.7%) are much higher than that in non-Hispanic whites (7.2%).^{vi} Complications are also often more frequent and more severe.^{vii} Diabetes in the Native American population is even higher, with age-adjusted prevalence of the Pima Indians in Arizona for men and women aged 45 to 74 years at 65% and 72% respectively.^{viii} In Australia, prevalence of diabetes among Indigenous Australians is also significantly higher than in the general Australian public. A community-based study in the Northern Peninsula area of Australia placed prevalence of diabetes in Torres Strait Islanders as high as 26%.^{ix} Urban Indigenous Australians also have a similarly high prevalence rate (20%).^x These are among the world's highest prevalence rates, following the US Pima Indians and Nauruans (24%).⁵ Globally, prevalence in developed countries (6.0%) is higher than developing countries (3.3%) and will remain so over the next 25 years, but the burden of this disease will fall primarily on the developing countries due to a 48% increase compared to a 27% increase in developed countries. By the year 2025, it is estimated that >75% of people with diabetes will reside in developing countries.⁵

All people with diabetes are at risk of developing diabetic retinopathy.^{xi}

Manifestation and treatment of diabetic eye disease

Much has been learned about diabetic eye disease over the past few decades,^{xii} from aetiology and pathophysiology to treatment efficacy and healthcare delivery. Well-defined clinical practice guidelines have been developed in both the US and Australia, public health programs have been implemented and attempts made to elucidate barriers to care for both the healthcare provider and the person with diabetes. Despite these efforts, diabetic eye disease remains a leading cause of

new-onset blindness in adults aged 20 to 74 years in the US^{xiii} and in adults aged 20 to 65 years in Australia.^{xiv,xv}

Diabetic retinopathy (DR) is a well-characterized, sight-threatening, chronic ocular disorder that eventually develops, to some degree, in nearly all patients with diabetes.^{xvi} The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) demonstrated that 80% of people with Type 2 diabetes of 20 years' duration will have at least some degree of DR.^{xvii} Up to 21% of people with Type 2 diabetes have retinopathy when they are first diagnosed with diabetes.¹⁶ 2.5% of the entire US population aged 18 or older (5.3 million) have DR at any point in time.^{xviii} Known duration of diabetes is the greatest determinant for the presence of DR, with poor glycaemic control the most critical risk factor for development and progression of DR.¹³ Other systemic factors such as concomitant hypertension, renal disease, elevated serum lipids, pregnancy and anaemia also play a role in management of DR.^{xix}

People with diabetes may not necessarily experience any visual symptoms until an advanced stage of DR. Even before any DR changes are clinically detectable, there are already pathophysiologic alterations in retinal blood flow^{xx} and loss of retinal pericytes^{xxi}. The earliest clinical findings are primarily due to microvascular abnormalities that result in microaneurysms, intraretinal haemorrhages, cotton wool spots and venous beading. The presence and extent of these classify the severity of non-proliferative diabetic retinopathy (NPDR) into mild NPDR, moderate NPDR, severe NPDR and very severe NPDR based on comparison with stereoscopic fundus photographic standards derived from the Early Treatment Diabetic Retinopathy Study (ETDRS) extension of the modified Airlie House classification.^{xxii} As DR progresses, retinal ischaemia resulting from the gradual loss of microvasculature induces proliferation of new vessels

on the optic disc (NVD) or elsewhere (NVE). The presence, location and extent of this proliferation as well as any accompanying vitreous or pre-retinal haemorrhage enable classification of proliferative diabetic retinopathy (PDR) into high-risk PDR or less than high-risk PDR.⁷ Increased vascular permeability can occur at any stage of DR, resulting in accumulation of fluid in the retina defined as macular edema (ME) if there is retinal thickening within 3,000 µm of the fovea. If ME is present ≤500 µm of the fovea, it is clinically significant (CSME) as it threatens the centre of vision.^{xxiii} The predominant cause of visual loss from DR is CSME or PDR.^{xxiv}

There is currently no cure for DR but landmark multi-center randomized clinical studies such as the Diabetic Retinopathy Study (DRS), Early Treatment of Diabetic Retinopathy Study (ETDRS) and Diabetic Retinopathy Vitrectomy Study (DRVS) have established the treatment efficacy of photocoagulation and vitrectomy for reducing the risk of visual loss that would otherwise occur in the absence of treatment.¹⁹ This included finding a 50 to 60% reduction in the risk of severe visual loss in eyes with severe NPDR or PDR treated with panretinal photocoagulation.^{xxv}

Overall, timely and appropriate detection, treatment with laser photocoagulation and follow-up can reduce the risk of severe vision loss from PDR to less than 5% of patients.^{xxvi} Yet despite this knowledge, translating this into reality has been difficult primarily due to the lack of appropriate routine life-long ophthalmic care for people with diabetes.

In the US, several recent studies indicate that a large proportion of people with diabetes (35 to 79%)^{xxvii,xxviii,xxix,xxx,xxxi} are not attaining such care. This is also the case in Australia where the population-based Melbourne Visual Impairment Project (VIP) found that approximately 45% of people with diabetes are not accessing proper care at recommended intervals.^{xxxii} Harper et al.^{xxxiii}

found a similar proportion of people with diabetes in rural Victoria, Australia (48%; 559/1177) who had reported not having a dilated fundus examination within the past two years, including 29% (345/1177) who had never had a dilated fundus examination. The recent population-based Australian Diabetes, Obesity and Lifestyle Study (AusDiab) of 11,247 people including 475 people with diabetes found that 77% of diabetic participants reported having had an eye examination within the previous two years.^{xxxiv}

The ophthalmic health care needs of people with diabetes are currently unmet

Well-defined clinical practice guidelines in both the US and Australia emphasise the importance of regular eye examinations for people with diabetes. In the US, the American Diabetes Association, American Academy of Ophthalmology and American Optometric Association call for an annual comprehensive eye examination for all patients with diabetes.^{xxxv,xxxvi,xxxvii} Patients with Type 1 diabetes are recommended to have an initial ophthalmologic examination within three to five years after diagnosis once patients are 10 years or older^{xxxviii} and patients with Type 2 diabetes are recommended to have an initial examination at time of diagnosis since diabetes onset is more insidious and hence frequently not precisely known. In Australia, the National Health and Medical Research Council's clinical practice guidelines call for at least one eye examination every two years in patients with diabetes, with referral to an ophthalmologist and closer follow-up of 6 to 12 months if mild NPDR is detected.¹³ Regular eye examinations enables vision loss to be prevented by appropriate and timely treatment since visual loss that has already occurred cannot be reversed.¹⁷

Many cost-analyses in both US and Australia have demonstrated the clear benefit from the health care system's perspective if people with diabetes received the level of ophthalmic care

recommended by clinical practice guidelines. This is even without consideration of other factors such as quality of life and productivity, both of which have been found to be decreased in people with diabetes-related complications.^{xxxix, xl, xli, xlii} If 60% of all people with Type 1 and Type 2 diabetes in need of retinopathy treatment in the US receive that as recommended in the clinical trials, annual savings of US\$101.0 million and 47,374 person-years of sight^{xliii} and US\$247.9 million and 53,986 person-years of sight^{xliiv} respectively would be generated. If every single person with diabetes were to receive the recommended level of care, savings of \$624.0 million and 173,540 person-years of sight would be realized.¹⁹ In Australia, epidemiology-based models place the overall DR-related health care expenditure incurred by the Government at A\$193 million with annual savings of approximately A\$14.5 million if compliance with clinical practice guideline recommendations improved from 30% to 80% of people with diabetes.¹³

In order to increase the number of people with diabetes attaining ophthalmic care, studies have attempted to elucidate barriers faced by both the healthcare provider and the person with diabetes. Kraft et al.^{xliv} in their study of Primary Care Physicians (PCPs) in Indiana, USA found that self-reported DR-related practice patterns differed significantly from published guidelines with only 52% of physicians performing in-office ophthalmoscopy, of which 90% were done through undilated pupils. Almost 58% and 40% of physicians reported referring all their patients with Type 1 diabetes and Type 2 diabetes respectively to ophthalmologists. In Australia, 88% of General Practitioners (GPs) in Victoria reported that they referred their patients with diabetes to an ophthalmologist at the recommended frequencies. Of those who performed in-office ophthalmoscopy, 65% reported never dilating pupils.^{xlvi} The role of the physician in primary care settings should not be underestimated as Livingston et al.^{xlvii} in an Australian study reported that of the people with diabetes who self-reported a dilated fundus examination for evaluation of DR in the previous two

years, 61% indicated that their GP was the main prompt. People with diabetes often present to a variety of potential examiners such as GPs, physicians, nurses, endocrinologists, optometrists and ophthalmologists¹³ and a team approach to co-ordinated care may facilitate overcoming some barriers faced by the patient such as competing medical priorities.

To elucidate barriers faced by people with diabetes, studies have utilised demographic information, self-report of perceived barriers and/or Medicare claims data to evaluate the factors that increase the likelihood of seeking ophthalmic evaluation for DR. Implementation of a nationwide survey of the US civilian, non-institutionalised population ≥ 18 years of age by Brechner et al. found that only 49% of all adults with diagnosed diabetes had undertaken a dilated eye examination (DFE) the previous year.^{xlviii} Likelihood of Type 2 patients having a DFE increased with older age, higher socio-economic status and having attended a diabetes education class. Race, duration of diabetes, frequency of physician visits for diabetes or health insurance was not found to be independently associated with having a dilated eye examination. This differed from the WESDR findings by Moss et al.³⁴ where longer duration of diabetes and health insurance that covered eye examinations made patients more likely to have a DFE, as did more severe DR and a history of glaucoma or cataract. Similarly, only 64% and 62% of patients with diabetes onset < 30 and ≥ 30 years of age respectively reported a DFE in the previous year. Likelihood of having a DFE for patients with diabetes onset < 30 years of age was associated with older age, visual impairment, higher income and more education; female gender and more education increased likelihood for patients with diabetes onset ≥ 30 years of age. The AusDiab study reported type of diabetes treatment (odds ratio=4.17 for insulin with or without tablets versus diet alone) and visiting a diabetes nurse practitioner in the past twelve months as being independent predictors of having had an eye examination.³⁷

Some studies also additionally asked those patients who had *not* undertaken eye examinations in the previous year to articulate their personal reasons for this. Moss et al.³⁴ found that 79% and 71% of patients with diabetes onset <30 and ≥30 years of age respectively reported not having a DFE because they had no problems with their eyes; 31% and 35% respectively reported not having been told they needed one. 30% and 12% said they could not afford an examination. Comparing responses from those who *knew* that they should have an annual examination with those who did not know, only affordability was significant (p<0.005). The Diabetic Eye Disease Follow-up Study^{xix} also elucidated similar factors such as lack of knowledge about DR and limited finances as the primary reasons for non-adherence to guidelines. Klein noted the need to develop approaches for the detection of DR in those who do not have health insurance to cover such care.^l Yet it is interesting to note that in Australia where universal healthcare is available and patients do not have out of pocket expense for retinal examinations in public hospital clinics, only 61.1% in reported having seen an ophthalmologist in the past year.³⁵

In another Australian study, Sikivou et al.ⁱⁱ evaluated patients with diabetes presenting to a public metropolitan eye and ear hospital who did not have regular eye examinations and reported that 61% (77/126) identified lack of knowledge about the need for regular eye examinations or not having any symptoms as a barrier. Interestingly, 89% (112/126) reported having more than two barriers including 37% (47/129) who identified a combination of knowledge and other barriers such as lack of access, competing medical problems and language. Pasagian-Macaulay et al.ⁱⁱⁱ also reported patients being unaware that DR may be asymptomatic or that visual loss could be prevented. Anderson et al.ⁱⁱⁱⁱ in their study of low-income diabetic patients in North Carolina, USA found that increased understanding of self-care components and adherence to them were

associated with increased perception of quality of care and, in turn, better general health perceptions in these patients ($p < 0.01$).

Of those studies utilizing Medicare claims data to evaluate the characteristics of people with diabetes seeking DR evaluation, Wang and Javitt^{liv} analysed 175,015 people ≥ 65 years of age with physician-diagnosed diabetes in the US and found that 53% of this population had had ≥ 1 eye care visit in a one-year period. Age < 75 years, male gender, black race, high regional poverty and fewer ophthalmologist supply were related to a lower rate of eye care use. There was no association between eye care use and regional education level and optometrist supply. Mukamel et al.³² also found that younger male patients with diabetes were less likely to seek eye examinations. However, residence in an area of higher average education and frequency of visit to their PCP were also associated with increased likelihood.

Gary et al.^{lv} studied racial and ethnic differences in the healthcare experience of adult diabetic patients in the US found that ethnic minorities with diabetes report less healthcare insurance coverage ($p < 0.001$) and more cost-related barriers to healthcare utilization ($p < 0.003$) compared to non-Hispanic Whites even after adjustment for age, sex, income, education and insulin use. The population-based Salisbury Eye Evaluation (SEE) project involving 2520 people with diabetes aged ≥ 65 in Maryland, USA also found that African-Americans were significantly less likely to visit any eye care provider over one year compared to non-Hispanic Whites (50% versus 69%).³¹

Hence it is clear from the preceding discussion that there are indeed barriers to the optimal care of people with diabetes. Many programs and initiatives have been formulated and implemented in attempts to address these. With the advance of technology, telemedicine also heralds great

potential in its ability to reach communities that are currently receiving no or sub-optimal eye care due to geographic or socio-cultural isolation from the mainstream tertiary healthcare system.

The potential of telemedicine in ophthalmology

Telemedicine is defined as the “use of transmitted images, voice and other data to permit consultation, education and integration of medicine over a distance”.^{lvi} Ophthalmology has often been feted as a specialty to which telemedicine is especially suited, since ophthalmologists are already accustomed to diagnosing disease asynchronously from images, photographs and angiograms.^{lvii} The ability to transfer digital images of the fundus for remote evaluation has proved promising.

The impetus for developing telemedicine stem from its potential to extend tertiary or specialty care to populations in remote or under-served communities, to military personnel in a variety of locations^{lviii} and to state correctional facilities.^{lix} For example, Blackwell et al.⁵⁹ implemented a telemedicine study in the remote town of Mt Isa in Queensland, Australia where the nearest hospital with ophthalmic specialist consultation was 900 kilometres away in Townsville. Patients presenting to the local emergency department with acute eye conditions were examined by a local practitioner via slit lamp while a high-resolution televised image was simultaneously assessed by the ophthalmologist, in voice and visual contact with the patient and local practitioner. Due to this telemedicine initiative, the number of patients usually transferred to Townsville for urgent assessment decreased from 17 in the corresponding three-month period the previous year to 4 during the study period. Total cost savings of approximately A\$10,000 were generated but more importantly, it enabled patients to receive high-quality healthcare locally regardless of their geographic residence.

Under-served communities need not necessarily be geographically remote; they may be isolated due to socio-cultural and economic factors. For example, the tele-ophthalmology initiative by Charles Drew University of Medicine and Science^x addressed an under-served population residing in a public housing development of inner-city Los Angeles, California whose access to medical care was hampered by the closure of county clinics and lack of reliable public transportation. Local residents were trained as telemedicine technicians for the housing development-based eye clinic, and images acquired were forwarded to the university clinic for diagnosis by ophthalmologists. This is a promising example of how telemedicine can positively affect under-served communities by increasing their access to eye care services, but it is also a source of empowerment by having local imagers acquire new skills.

Other studies have also investigated the ability of tele-consultation to enhance peri-operative management of patients presenting for cataract surgery^{lx} and the usefulness of real-time fundus imaging via a direct ophthalmoscope fitted with a digital micro-camera for evaluating Acquired Immune Deficiency Syndrome (AIDS)-related retinopathy in Human Immunodeficiency Virus (HIV)-positive population.⁶² Telemedicine is also currently being trialled in a pilot study involving inmates in correctional facilities throughout Texas, USA.⁶⁰

Telemedicine and evaluation of diabetic eye disease: the Joslin Vision Network

Much research has been directed at developing telemedicine for evaluation of DR in view of the evidence-based efficacy of early detection and the high burden of disease caused by diabetes in the community. From a public health perspective, Vinicor^{lxii} proposes a model with four transition points or opportunities within the life history of a person with diabetes during which the burden of

disease may be reduced. Telemedicine offers the opportunity to take action at both level three and four by enhancing access and utilization as well as quality of care. (Figure 1)

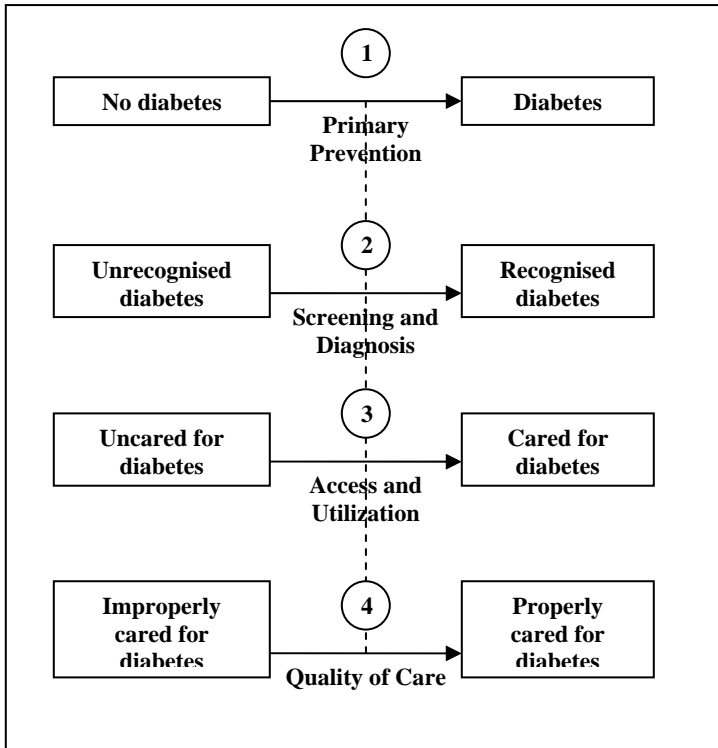


Figure 1: The four clinical transition points in the natural history of an individual with diabetes⁶⁵

Examples of telemedicine programs for DR evaluation include that by Cummings et al.^{lxiii} in which non-mydratic digital fundus images were acquired from patients with diabetes in rural North Carolina, USA and electronically forwarded to a retinal specialist for diagnosis. Patients' acceptability of this technology was high, with 96.3% of patients being reportedly "very comfortable" or "comfortable" with the technology.

Rotvold et al.^{lxiv} in Norway reported similarly high patient satisfaction in a pilot study with patients with Type 2 diabetes. Other tele-ophthalmology initiatives for DR evaluation have been implemented in First Nations^{lxv} and Inuit populations^{lxvi} of Canada.

The Joslin Vision Network (JVN) is the telemedicine initiative of the Joslin Diabetes Center with its primary aim to facilitate patients with diabetes into chronic disease management within the Joslin Diabetes Eye Health Care Model. Components of this model encompass non-mydratic digital retinal imaging and telemedicine outreach via the JVN platform as well as diabetes care education.

By dispensing with the need for pharmacological pupil dilation and utilising telemedicine outreach, the JVN has the ability to enhance access and utilisation of eye care services by people with diabetes currently receiving sub-optimal or no eye care. This is evident from evaluation of the JVN programs at the Tripler Army Medical Center in Hawaii^{lxvii} as well as at the Veterans Affairs Medical Center in Togus, Maine.^{lxviii,lxix} Importantly, the JVN has also enabled appropriate triage and prioritization of eye examinations based on DR severity as determined by the ETDRS extension of the modified Airlie House classification. This distinguishes it from other DR evaluation programs that may use a less stringent criterion for grading such as “presence or absence of retinopathy” or a “referral threshold”. It is not intended to replace a comprehensive eye examination, but rather to enhance access by overcoming barriers and appropriately prioritizing those in most need for urgent ophthalmic assessment and care.

The ability to train non-physician imagers and graders as part of the JVN clinical pathway also enables limited resources such as ophthalmologists to be allocated to those most in need of urgent ophthalmic evaluation and treatment. Training local residents as JVN imagers may also improve its ability to deliver culturally sensitive initiatives to differing communities. For example, Asian-Americans are the lowest represented ethnicity at the Joslin Diabetes Center (Personal communication, Paula Katalinic, 2003) and hence a JVN program was implemented within the South Cove community clinic in inner-city Boston where a high proportion of Chinese-American people with diabetes reside.

In order to ensure its validity for evaluation of DR, Bursell et al.¹ compared JVN imaging with the current gold standard for DR evaluation of ETDRS 7-standard field photography and found substantial ($\kappa=0.65$) with for clinical levels of DR. The JVN has also compared favourably with

dilated clinical examination by retinal specialists, with exact agreement for clinical level of DR in 72.5% (388/535) of eyes and within one level in 89.3% (478/535) of eyes.² Interestingly, Cavallerano et al.² noted that 25.9% (136/525) of patients had ocular abnormalities other than DR requiring referral for a comprehensive eye examination. The JVN is also currently incorporated within the clinical program of Joslin's Diabetes Outpatient Intensive Treatment (DO IT) Program.

PURPOSE OF THIS STUDY

The JVN has been validated as a platform for evaluation of DR. The purpose of this study is to utilise the validated JVN imaging platform to determine the extent and diversity of lesions other than DR in people with diabetes, comparing its ability to detect such lesions with ETDRS 7-standard field photography and dilated clinical examination by retinal specialists.

Part One: Joslin Diabetes Center (Boston, USA)

- To characterize the extent and diversity of non-DR ocular findings in a population of patients with diabetes presenting for care in a tertiary healthcare institution.
- To evaluate the ability of the JVN to detect non-DR pathology compared with dilated clinical eye examination by retinal specialists ophthalmologists.
- To characterise the agreement between the JVN and dilated clinical examination for levels of DR for comparison to other JVN studies.

Part Two: Centre for Eye Research Australia (Melbourne, Australia)

- To characterize the extent and diversity of non-DR ocular findings in a population of patients with diabetes presenting for care in a tertiary healthcare institution.

- To evaluate the ability of non-stereoscopic non-mydriatic single-field digital retinal imaging to detect non-DR compared with the gold-standard of stereoscopic mydriatic ETDRS 7-standard field fundus photography.

IMPLICATIONS OF THIS STUDY

Characterising the extent and diversity of non-DR lesions in a population of patients with diabetes in the US and Australia adds to the body of knowledge that as serious as DR is as a medical and public health problem, non-DR ocular pathology also contributes to the health and wellbeing of a person with diabetes. Chronic open-angle glaucoma, cataract^{lxx, lxxi, lxxii} and diabetic ischaemic optic neuropathy have previously been noted as non-DR disorders that can cause blindness in the diabetic population.^{lxxiii} Cataract is the most common cause of visual impairment in patients whom diabetes was diagnosed at ≥ 30 years of age.^{lxxiv} Mitchell et al.^{lxxv} in the Blue Mountains Eye Study also could not rule out the possibility of an association between diabetes and late age-related macular degeneration.

Comparison of digital retinal imaging without pupil dilation within the JVN telemedicine platform with dilated clinical examination will enable preliminary evaluation of its ability to detect non-DR findings. This will aid planning of additional prospective studies to fully validate these findings. A telemedicine platform such as the JVN that is able to accurately and efficiently triage patients with consideration of both DR and non-DR ocular findings will ensure improved quality of care for individuals with diabetes.

Comparison of digital retinal imaging without pupil dilation with stereoscopic mydriatic ETDRS 7-standard field photography in Melbourne, Australia will also enable evaluation of its ability

compared with the gold-standard for detection of diabetic eye disease. This may aid further studies wishing to utilise non-mydratic digital retinal imaging for epidemiological or clinical purposes. Australia is a vast land with a low population density (2.5 people per square kilometre) and approximately 250 Statistical Local Areas with <1 person per square kilometre.^{lxxvi} (Figure 2) Non-mydratic digital retinal imaging and telemedicine has the potential to facilitate access and utilisation of healthcare by those currently receiving sub-optimal or no eye care. This study hopes to add knowledge towards implementing initiatives that strive to improve this imbalance.

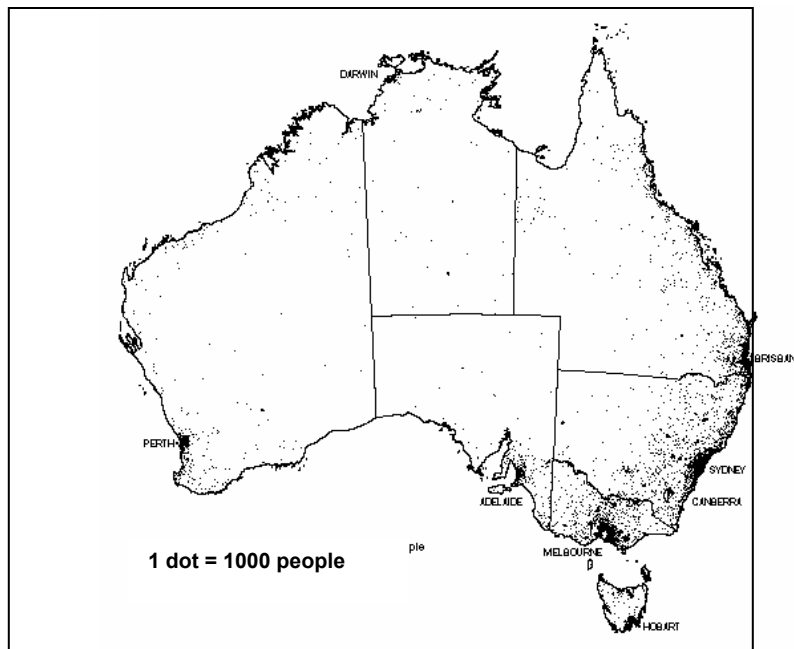


Figure 2: Population distribution of Australia⁷⁹ (2003)

Methodology

PART ONE: JOSLIN DIABETES CENTER (BOSTON, USA)

STUDY POPULATION

Between 1st January and 31st July 2003, 960 patients new to the Joslin Diabetes Center's outpatient clinic underwent non-mydratic digital retinal imaging with the Joslin Vision Network (JVN) as part of their first visit to their diabetes care team. 306 patients (31.9%) were subsequently referred for a comprehensive dilated eye examination with a retinal specialist ophthalmologist at the Beetham Eye Institute (BEI) of Joslin Diabetes Center. Reasons for referral included identification of significant retinal disease (defined as severe or worse NPDR, any PDR, diabetic macular edema, non-diabetes-related ocular findings, or unreadable images).² Patients with >1 year since their last eye examination or at the patient's request were also offered the opportunity of a comprehensive eye examination.

Of 306 patients scheduled for an eye examination, 289 patients (94.4%) undertook a comprehensive eye examination with a BEI retinal specialist ophthalmologist. Retrospective chart review compared findings from all 289 patients' medical records with findings from their JVN Evaluation Report. Patients were excluded from this study if they did not have a confirmed diagnosis of diabetes mellitus as defined by the American Diabetes Association^{lxvii} (n=9), leaving 280 patients.

RESEARCH DESIGN AND DATA COLLECTION

Patients new to the Joslin Diabetes Center's outpatient clinic were contacted via telephone by the JVN Clinical Team prior to their first appointment with their diabetes care team and offered a 15-minute imaging session with the JVN system as an adjunct to their first visit. Upon arrival, patients signed an institutionally approved consent/waiver that included a statement explaining that the JVN evaluation did not replace a comprehensive eye examination. Each patient's demographic information, relevant diabetes and medical history including duration of diabetes and date of last dilated eye examination were obtained and recorded. The importance of regular eye examinations was emphasized.

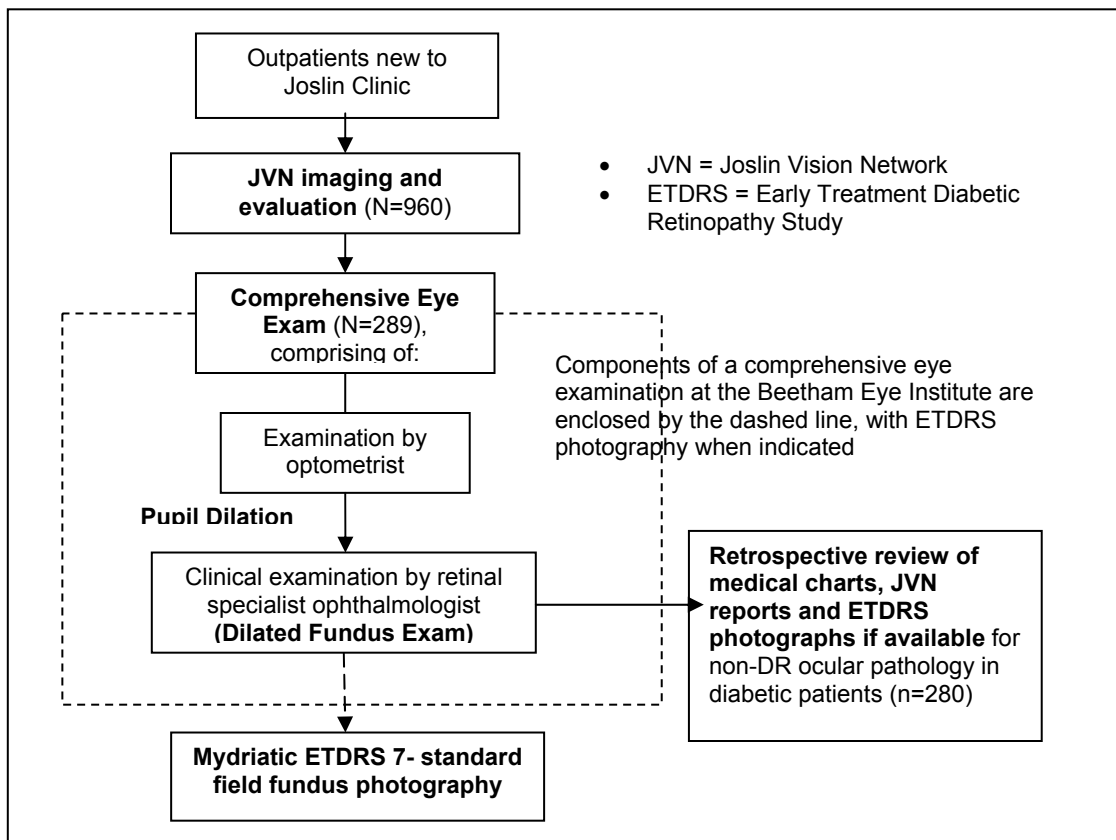


Figure 3: Research design and data collection at Joslin

Non-mydriatic digital retinal imaging with the JVN

Certified JVN Imagers then obtained color, non-simultaneous stereoscopic digital retinal images in a darkened room to enhance physiological pupil dilation. No pharmacologic pupil dilation was undertaken. The JVN images consisted of three 45⁰ retinal fields, encompassing (1) the posterior pole including the macula and optic disc; (2) retina superior temporal to the optic disc and (3) retina nasal to the optic disc as per to JVN protocol.^{1,2,3} An external image of each eye showing the orbital adnexa and pupillary red reflex was also taken. Immediate feedback of the images on the integrated JVN imaging workstation and monitor enabled poor quality images to be re-taken in the same consultation if necessary. Images were captured with a non-mydratic fundus camera (Topcon® TRC NW-5S, Paramus, NJ) interfaced with a color video camera (Sony 970-MD) and optimized for low-light imaging to capture single-frame images of the retina. Images were then digitized, compressed and stored on the JVN system as described in detail elsewhere¹ before being electronically transmitted to the JVN Reading Center at the BEI for evaluation.

DILATED FUNDUS EXAMINATION BY RETINAL SPECIALISTS

Patients who presented for a comprehensive eye examination at the BEI first underwent optometric assessment including best-corrected visual acuity testing. Pupils were then pharmacologically dilated with 2.5% phenylephrine and 1% tropicamide. A BEI retinal specialist ophthalmologist performed a comprehensive dilated fundus examination (DFE) via indirect ophthalmoscopy and contact lens fundoscopy as indicated. The examining physicians did not have the JVN results prior to DFE. Patient may also be referred for further documentation of their ophthalmic status via ETDRS 7-standard 30⁰ field stereoscopic color fundus photography. These were taken by a certified ophthalmic photographer with a Zeiss (FF4) 30⁰ mydratic fundus camera (Zeiss Humphrey Systems, Dublin, CA) using 35-mm Kodachrome 64-color slide film (Eastman Kodak Co., Rochester, NY). The 35-mm slides were then processed through the BEI Photography

Department according to standard clinical practice and ETDRS Reading Center protocol^{lxviii} and placed in the patient's medical record for further review.

Grading of images and Adjudication

JVN images were evaluated at the JVN Reading Center by a certified JVN Reader for diabetes-related and non-diabetes-related ocular pathology. Each patient's images were reviewed on a 21-inch monitor (resolution of 1280 x 1024 x 24 bits) in a darkened room. Stereoscopic image viewing was enabled through Liquid Crystal Display (LCD) shuttered goggles (Stereographics, San Rafael, CA). Each image was graded for specific lesions of DR such as hemorrhages and microaneurysms (H/Ma), hard exudates (Hex), venous beading (VB), intraretinal microvascular abnormalities (IRMA), soft exudates, neovascularization and fibrous proliferation in the optic disc region (NVD) or elsewhere in the retina (NVE). Non-DR ocular pathology was also noted in a text box labeled "Additional Findings". All findings were electronically entered into a JVN template (findings template), from which JVN software calculated the clinical level of DR based on ETDRS-derived algorithms (diagnosis template). A recommended examination schedule is also generated from the diagnosis template. A summary of results from each JVN evaluation including

Microsoft Access
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Jan1 thru July31 2003 NC Patients n=961

JDC # Last Name First Name Gender
Birthdate Onset of DM HbA1c Exam Overdue

JVN Imaging Report
JVN Imaging Date

OD OS Other Findings

	OD	OS	OD	OS
Level of NPDR			<input type="checkbox"/>	<input type="checkbox"/>
Level of PDR			<input type="checkbox"/>	<input type="checkbox"/>
Macular Edema			<input type="checkbox"/>	<input type="checkbox"/>
Previous Laser			<input type="checkbox"/>	<input type="checkbox"/>
Unable to Image	<input type="checkbox"/>	<input type="checkbox"/>		
Images Unreadable	<input type="checkbox"/>	<input type="checkbox"/>		

Other Referable Findings Present OD OS

Exam Sched JVN Treatment Plan

Additional Findings

- AMD
- Asteroid Hyalosis
- Cataract
- Choroidal Lesion
- Corneal Arcus
- C-R Atrophy/Scar
- Epiretinal Membrane
- IOL
- Iris Nevus
- Suspicious Lid Lesion
- Macular RPE/Drusen Changes
- Optic Nerve Head Drusen
- Other Misc. Anterior Segment Lesion
- Other Misc. Vitreous, Retinal or Choroidal Disorder
- PPA
- Renal/Hypertensive Retinopathy
- RPE Changes
- RRD
- TRD
- VH/PRH
- C/D Asymmetry

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patient

Figure 4: Electronic JVN template used in this study to document DR and non-DR findings in patients following JVN evaluation

and their diabetes physician.

Data from all 280 eligible patients' JVN evaluation including the clinical level of DR generated in the JVN diagnosis template and non-DR ocular findings noted in the "Additional Findings" text box was entered into an Access database. (Figure 4) An independent research associate with no previous contact with this patient cohort and masked to their ocular findings then reviewed each of these 280 patients' medical records to note the level of DR and any non-DR findings documented by the retinal specialist. This information was entered into an identical Access database without reference to the findings from the JVN evaluation. At the completion of data entry, the Access databases were linked and analysis of data undertaken. (Refer to Appendix 1 for full template used for this study to compare DR and non-DR findings from JVN reports and medical charts)

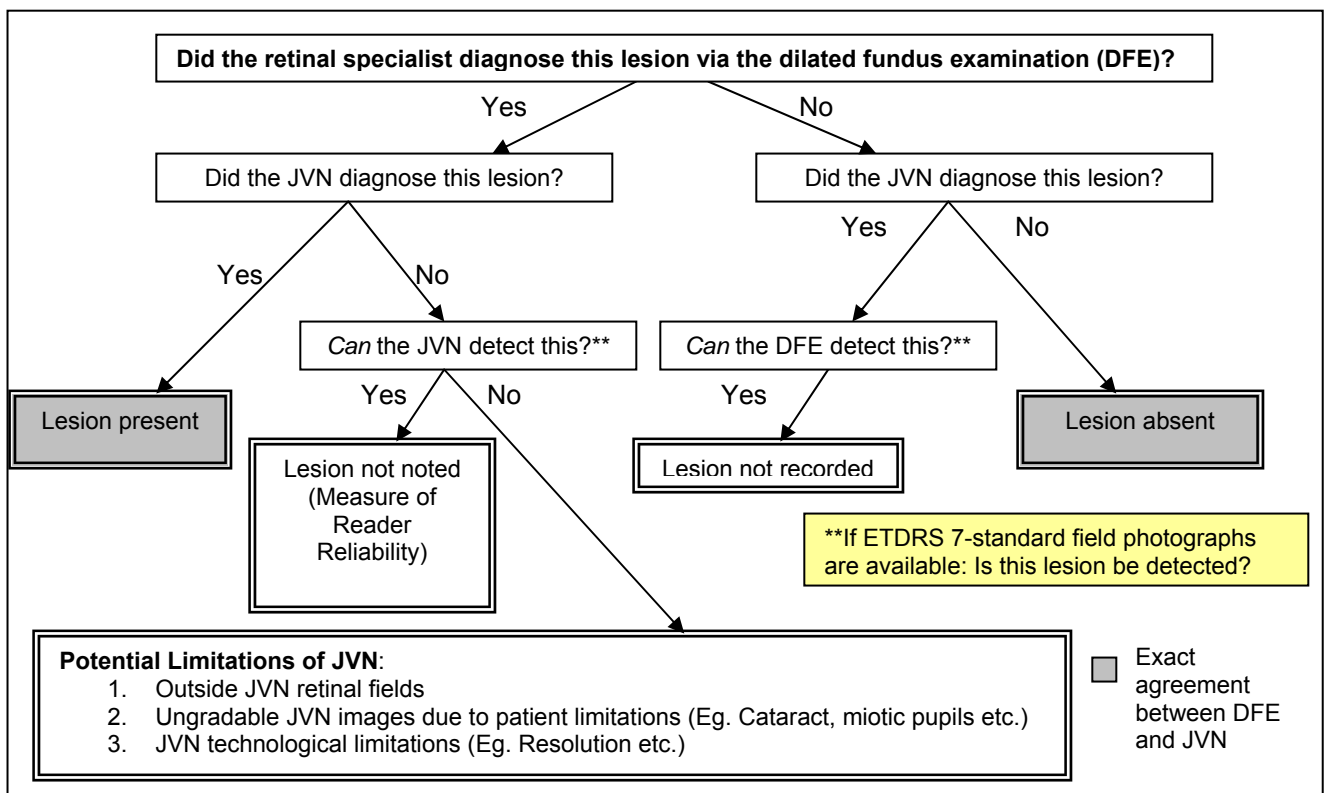


Figure 5: Algorithm for adjudication of disagreements

Disagreements were adjudicated by an independent senior retinal specialist (L.M.A.) through review of available ETDRS photographs, JVN images stored on the JVN system and also medical charts to elucidate possible reasons for disagreement. The algorithm in Figure 5 was used as a guideline for adjudication.

PART TWO: CENTRE FOR EYE RESEARCH AUSTRALIA (MELBOURNE, AUSTRALIA)

STUDY POPULATION

Between 1st January and 31st July 2003, patients with diabetes from the Retina and Primary Care Clinics at the Royal Victorian Eye and Ear Hospital in Melbourne, Australia were invited to participate in a study^{lxxix} comparing three modalities for detection of DR: The use of a non-mydriatic camera to undertake digital retinal images versus one optimized for Polaroid film against the gold standard of mydriatic ETDRS 7-standard field fundus photography. Patients were eligible if they were 18 years or older, had a self-reported diagnosis of diabetes of any duration and was willing to sign the institutionally approved consent form. The study was approved by the Ethics Committee of the Royal Victorian Eye and Ear Hospital. From that study population, data available from all 141 patients who had undertaken both digital retinal imaging and ETDRS photography were reviewed for any non-diabetes-related (NDR) ocular pathology. Patient details were de-identified and study participant numbers assigned. Each patient's demographic information and diabetes status were obtained from that patient's medical records.

RESEARCH DESIGN AND DATA COLLECTION

Imaging protocol for digital retinal images and ETDRS 7-standard field photographs

The imaging protocol for the digital images was similar to that at Joslin in not utilizing any pharmacologic pupil dilation. However, in the Melbourne study, only one 45⁰ single-field digital image centered on the posterior pole including both the macula and optic disc was taken per eye compared with the JVN's three 45⁰ retinal fields. Unlike the (non-simultaneous stereoscopic) JVN images, these images were not stereoscopic. Main differences are summarized in Table 1.

Images were captured with a non-mydratic fundus camera (Canon CR6-NM, Tochigi-ken, Japan) connected to a laptop (Dell Precision M50 notebook) with a processing speed of 1.8 Ghz and 1 GB of RAM. The monitor was optimized for high resolution imaging. Flash power of the camera was set at "low". High resolution of 2160 x 1440 pixels was achieved in true color. Each file achieved a resolution of 3.25 megapixels. Images were viewed and archived with DHClient software (Digital Healthcare, Sydney, Australia).

	JVN protocol	Melbourne protocol
Requires pupil dilation?	No	No
Digital imaging?	Yes	Yes
Stereoscopic?	Yes	No
Number of fields	Three 45 ⁰ fields	One 45 ⁰ field
Advantages	<ul style="list-style-type: none">▪ Telemedicine capability	<ul style="list-style-type: none">▪ Portability▪ Lower cost of implementation

Table 1: Main differences in imaging protocols between the JVN and Melbourne study

It should be noted that the emphasis of this imaging protocol is to deliver healthcare in the most mobile, cost-effective means. Imaging protocol for obtaining mydratic stereoscopic ETDRS 30⁰ 7-standard field fundus photography has been described in Part One.

Grading of images and Adjudication

Digital images were first evaluated for non-DR findings by a trained non-physician reader before being confirmed by an ophthalmologist. Both the ophthalmologist and non-physician reader was masked to any knowledge of non-DR findings in the patients. Each patient's images were reviewed on a 21-inch monitor (resolution of 1280 x 1024 x 24 bits). Findings were entered into an Access database.

ETDRS photographs were first evaluated by a trained non-physician reader before being reviewed by a retinal specialist ophthalmologist. Slides were read over a standard light box with a +10-dioptre Donaldson binocular stereoscopic viewer. The retinal specialist was masked from any knowledge of the findings from the digital images. All disagreements were adjudicated through review of ETDRS photographs and digital images.

ANALYSIS OF DATA

Statistical analysis was performed with SPSS Version 11.0 (SPSS, Chicago, IL). Descriptive statistics were used to characterize the study population. Overall agreement between the two modalities for each non-DR finding was calculated in both cohorts. The Kappa statistic (unweighted), which measures the degree of agreement over and above that expected by chance alone^{lxxx}, was also used to evaluate agreement between JVN non-mydratic digital imaging and dilated fundus examination by retinal specialists. Landis and Koch's recommendations for unweighted Kappa interpretations were used: No agreement ($\kappa < 0$); poor agreement ($\kappa = 0.00 - 0.19$); fair agreement ($\kappa = 0.20 - 0.39$); moderate agreement ($\kappa = 0.40 - 0.59$); substantial agreement ($\kappa = 0.60 - 0.79$) and nearly perfect agreement ($\kappa = 0.80 - 1.00$).^{lxxxi} The ETDRS adopted this scale for weighted Kappa statistics as well.²⁵ Kappa values were also calculated for the Melbourne cohort.

Results

PART ONE: JOSLIN DIABETES CENTER, BOSTON, USA

STUDY POPULATION

OF THE 280 PATIENTS WITH DIABETES MELLITUS WHO UNDERWENT BOTH DILATED FUNDUS EXAMINATION (DFE) AND JOSLIN VISION NETWORK (JVN) IMAGING, 122 (43.6%) WERE FEMALE AND 83 (29.6%) HAD TYPE 1 DIABETES. AVERAGE AGE AT JVN IMAGING WAS 50.7 ± 15.2 YEARS (RANGE: 20.3 TO 84.4 YEARS). AVERAGE DURATION OF DIABETES WAS 10.8 ± 9.8 YEARS (RANGE: 0 (DAY OF DIAGNOSIS) TO 49 YEARS). AVERAGE INTERVAL BETWEEN JVN IMAGING AND DFE WAS 39.6 DAYS (SD=43.5; MEDIAN=24.0 DAYS; RANGE: 1 TO 250 DAYS).

DIABETES-RELATED FINDINGS

CLINICAL LEVEL OF DIABETIC RETINOPATHY

Severity of diabetic retinopathy (DR) was distributed across all levels. Of 560 eyes from 280 patients, there were 259 eyes (46.3%) with no clinical level of diabetic retinopathy, 101 eyes (18.0%) with mild NPDR, 78 eyes (13.9%) with moderate NPDR, 38 eyes (6.8%) eyes with severe or very severe NPDR to 29 eyes (5.2%) with any proliferative diabetic retinopathy. (Table 2)

JVN images were deemed not gradable for DR in 55 eyes (9.8%), primarily due to cataract (n=25; 45.5%). Other causes included the presence of small pupils (n=9; 16.4%), history of extensive

panretinal photocoagulation (n=2; 3.4%), history of trauma and correctopia (n=1, 1.8%) and “poor fixation due to chorio-retinal scar” (n=1, 1.8%). Reasons were not specified for 20 eyes (36.4%). All patients with JVN retinal fields that were not gradable are automatically indicated for referral to an ophthalmologist.

Level of diabetic retinopathy (DR)	JVN evaluation		Clinical examination	
	Number of eyes (n=560)	Number of patients* (N=280)	Number of eyes (n=560)	Number of patients* (N=280)
No DR	259 (46.3%)	121 (43.2%)	282 (50.4%)	136 (48.6%)
Mild NPDR	101 (18.0%)	52 (18.6%)	135 (24.1%)	71 (25.4%)
Moderate NPDR	78 (13.9%)	39 (13.9%)	73 (13.1%)	35 (12.5%)
Severe or very severe NPDR	38 (6.8%)	20 (7.1%)	29 (5.2%)	15 (5.4%)
• Severe NPDR	34 (6.1%)	17 (6.1%)	26 (4.6%)	13 (4.6%)
• Very severe NPDR	4 (0.7%)	3 (1.1%)	3 (0.5%)	2 (0.7%)
Proliferative DR	29 (5.2%)	17 (6.1%)	41 (7.3%)	23 (8.2%)
• PDR <HRC	16 (2.9%)	9 (3.2%)	24 (4.3%)	12 (4.3%)
• PDR with HRC	7 (1.3%)	5 (1.8%)	3 (0.5%)	4 (1.4%)
• Quiescent PDR	6 (1.1%)	3 (1.1%)	14 (2.5%)	7 (2.5%)
Cannot grade	55 (9.8%)	31 (11.1%)	0 (0%)	0 (0%)

*By diagnosis in the worse eye

Table 2: DR severity as identified by JVN / Non-mydratric digital imaging evaluation

Of the 505 gradable images, there was exact agreement between JVN imaging and dilated fundus examination (DFE) by a retinal specialist for the exact clinical level of DR in 381 eyes (75.5%). An additional 109 eyes were diagnosed within one level of DR, elevating agreement between JVN and DFE to 97.0% (490/560) of all gradable eyes. Overall, JVN diagnosis was more severe than indicated on DFE in 75 eyes (14.9%) and DR level was noted as being less severe in 49 eyes (9.7%).

Clinical exam	JVN evaluation									
	No DR	Mild NPDR	Mod NPDR	Severe NPDR	V.Severe NPDR	<HR-PDR	HR-PDR	Qt	CG DR	
No DR	236	22							24	282
Mild NPDR	23	62	35			1			14	135
Mod NPDR		15	40	9	3	2			4	73
Severe NPDR			2	21			1		2	26
Very Severe NPDR			1	1	1					3
<HR-PDR		1		3		12	2		6	24
HR-PDR							3			3
Quiescent		1				1	1	6	5	14
CG DR									0	
	259	101	78	34	4	16	7	6	55	560

Mod=moderate; Qt=Quiescent

Table 3: Agreement in severity of DR

When ungradable JVN images are included, the level of exact agreement was 68.0% and diagnosis within one level of DR was 87.5%. Among all eyes evaluated, eight eyes (1.4%) disagreed by two levels of DR, and a further six (1.1%) disagreed by more than two levels. Of those that disagreed by more than two clinical levels of DR, JVN diagnosis was more severe than indicated on DFE in 4 eyes (66.7%) and less severe in 2 eyes (33.3%).

DIABETIC MACULAR EDEMA

JVN evaluation identified 59 eyes (10.5%) with diabetic macular edema (DME). This diagnosis was based on the presence of retinal thickening or hard exudates within 3000 µm from the centre of the macula, and included both Early Treatment Diabetic Retinopathy Study (ETDRS) criteria of clinically significant macular edema (CSME)^{lxviii} as well as ME <CSME. Of 560 total eyes, 85 eyes (15.2%) were deemed not gradable for DME. Of eyes with ungradable images, DFE identified 43 of these (81.2%) as being absent of DME; 9 eyes with CSME and 4 eyes with DME without meeting criteria for CSME. The retinal specialist also noted inability to grade DME in one eye and did not note the status of DME in two eyes.

Clinical exam	JVN evaluation				
	Absent	DME <CSME	CSME	CG ME	
Absent	405	12	2	69	488
DME <CSME	9	12	11	4	36
CSME	1	1	21	9	32
CG ME	1			1	2
	416	25	34	85	558

CG=cannot grade; NR=ME status not recorded for 2 eyes

Table 4: Agreement for diagnosis of macular edema

Of all gradable images (n=475), there was exact agreement between JVN evaluation and DFE in 439 eyes (92.4%). When JVN images not gradable for DME were included, the level of exact agreement is 78.4%. JVN evaluation identified 416 eyes with absence of any DME and the retinal specialist agreed exactly with this diagnosis in 405 eyes (97.4%). For the presence of DME, there was exact agreement between JVN evaluation and DFE in 45 eyes (76.3%) with JVN evaluation identifying 34 eyes with presence of CSME. Of these 34 eyes, the retinal specialist agreed exactly with 21 eyes (61.8%) and diagnosed the presence of DME not meeting criteria for CSME in a further 11 eyes (32.4%).

NON-DIABETES-RELATED FINDINGS

Of all patients, 40.7% (114/280) in the Joslin cohort had at least one non-DR finding. The diversity and extent of these non-DR findings are outlined in Table 5.

Non-DR ocular finding	JVN cohort Number of eyes=560 (%)		Melbourne cohort Number of eyes=279 (%)	
	Non-mydrriatic digital images	Clinical examination	Non-mydrriatic digital images	ETDRS 7-std field photos
Cataract	74 (13.2%)	100 (17.9%)	40 (14.3%)	36 (12.9%)
AMD, macular drusen and/or RPE changes	67 (12.0%)	39 (7.0%)	24 (8.6%)	39 (14.0%)
Suspicion of glaucoma	15 patients (5.4%)	16 patients (5.8%)	4 patients (2.9%)	8 patients (5.7%)
Hypertension, renal disease and other systemic risk factors for retinopathy	15 patients (5.4%)	10 patients (3.6%)	N/A	N/A
Epiretinal membrane	10 (3.6%)	10 (3.6%)	0 (0%)	3 (1.1%)
Choroidal lesion	18 (3.2%)	21 (3.8%)	2 (0.7%)	5 (2.5%)
C-R atrophy and/or scar	6 (1.1%)	8 (1.4%)	2 (0.7%)	4 (1.4%)
Retinal emboli	3 (0.5%)	3 (0.5%)	0 (0.0%)	0 (0%)
Retinitis pigmentosa	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Asteroid hyalosis	1 (0.2%)	1 (0.2%)	1 (0.4%)	1 (0.4%)
Macular hole	N/A	N/A	2 (0.7%)	2 (0.7%)

Bilateral myopic degeneration of the optic disc	N/A	N/A	2 patients (1.4%)	3 patients (2.1%)
CRVO or BRVO	0 (0.0%)	0 (0%)	1 (0.3%)	4 (1.4%)

N/A = Not Assessed for these non-DR lesions

0 = non-DR lesions were assessed but no cases were detected in cohort specified.

Table 5: Prevalence of non-DR findings as detected by differing modalities in this study

The overall agreement for these non-DR findings are presented in Figure 6.

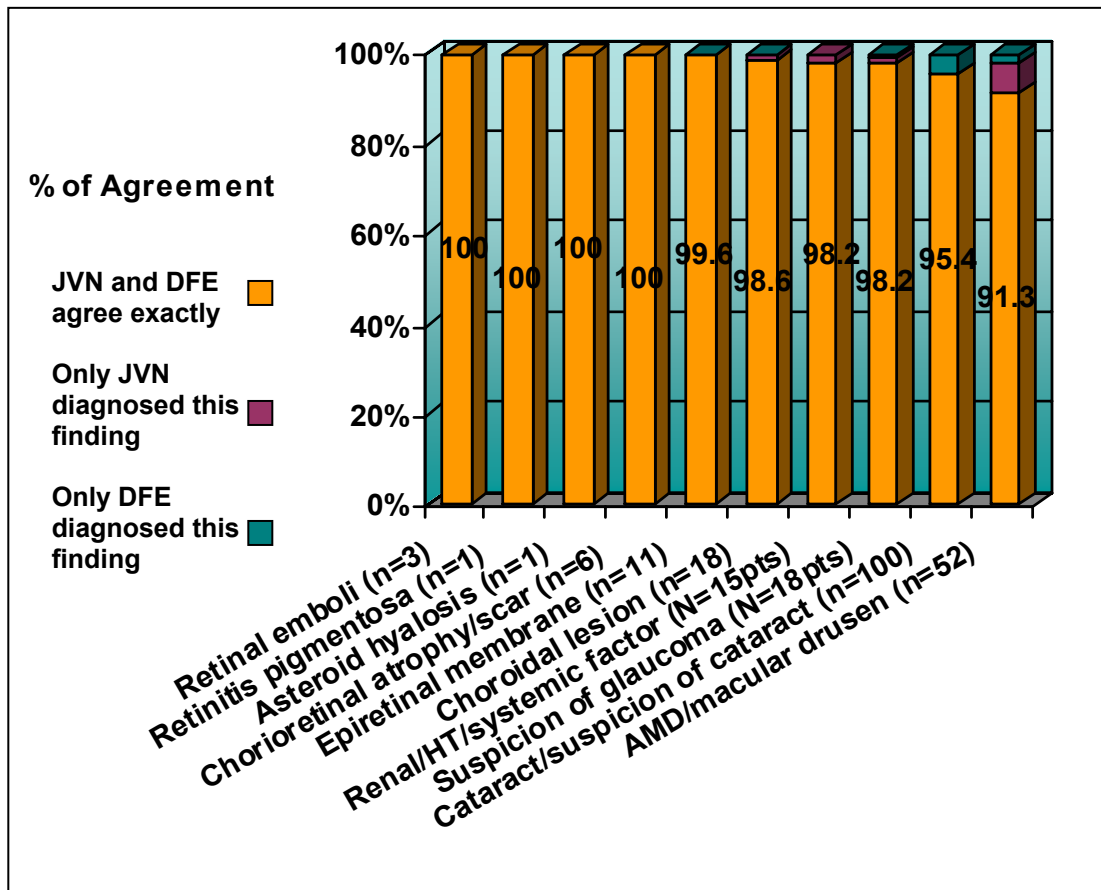


Figure 6: Exact agreement for non-DR findings within JVN fields in total eyes (n=560)

Level of agreement for each specific non-DR findings are detailed below. Kappa values are summarized and presented in Figure 13.

Retinal Emboli

There was exact agreement between DFE and JVN evaluation for the presence and absence of retinal emboli in 560 eyes (100%) ($\kappa=1.00$). JVN evaluation identified findings consistent with retinal emboli in three patients (3/280, 1.1%), hence triggering an urgent referral to a retinal specialist. The DFE confirmed these findings in all three patients (100%). The DFE did not note any other patient with findings consistent with retinal emboli in this cohort.

Chorio-retinal atrophy or scar

There was exact agreement between DFE and JVN imaging for the presence or absence of chorio-retinal atrophy and/or scarring in 558 (99.6%) eyes. DFE reported 8 eyes with presence of chorio-retinal atrophy and/or scarring; of the 6 eyes in which the lesion(s) fell within the fields of JVN images, JVN reported the lesion(s) in all 6 eyes (100%). The lesions reported in the remaining two eyes were confirmed to be outside JVN image fields in both cases as well as outside the ETDRS 7-standard fields, which were available for one of these cases. Agreement was perfect within JVN fields ($\kappa=1.00$) and almost perfect ($\kappa=0.86$) for all cases detected by DFE.

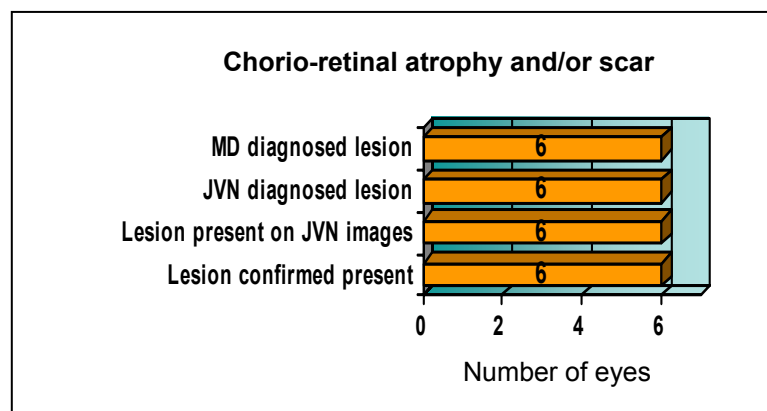


Figure 7: Agreement for chorio-retinal atrophy and/or scar

Choroidal lesion

There was exact agreement between DFE and JVN imaging for the presence or absence of choroidal lesion(s) in 543 (97.0%) eyes. Of 560 eyes, DFE reported 21 eyes (3.8%) with the presence of at least one choroidal lesion; of the 11 eyes (52.4%) in which the lesion(s) fell within JVN image fields, 10 (90.9%) were noted by the JVN reader although review of the JVN images revealed the presence of the lesion(s) in all 11 eyes (100%). Of the ten eyes with lesions outside JVN fields, ETDRS seven standard field photography was available for 6 eyes (60%): 2 eyes' lesion fell within the seven standard fields but not within JVN fields while 4 cases fell outside of both the seven standard fields and JVN fields. Additional to the 21 eyes reported by the ophthalmologist following DFE, JVN noted 7 more eyes with a choroidal lesion. Adjudication of these seven disagreements revealed the presence of choroidal lesion(s) in JVN images for all seven eyes. Hence, in the 18 eyes in which the choroidal lesion(s) fell within JVN fields, JVN images demonstrated all 18 (100%) but noted 17 (94.4%) while the ophthalmologist only noted 11 (61.1%). Agreement was substantial within JVN fields ($\kappa=0.73$) and moderate ($\kappa=0.55$) for all lesions detected by DFE.

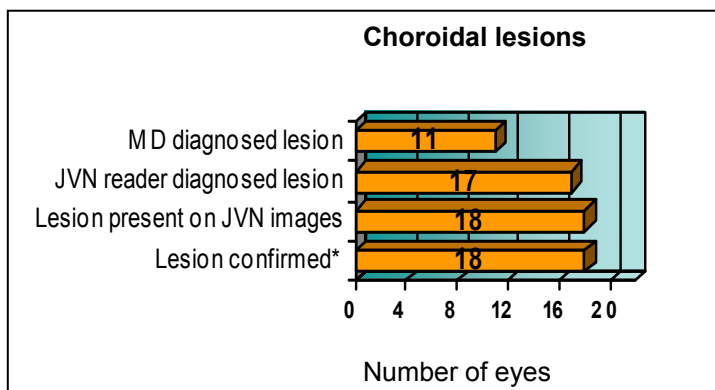


Figure 8: Agreement for choroidal lesions

Epiretinal membrane

There was exact agreement between DFE and JVN imaging for the presence or absence of an epiretinal membrane (ERM) in 558 eyes (99.6%). Agreement was almost perfect ($\kappa=0.95$). DFE noted the presence of ERM in 10 eyes (1.8%). Of the 9 eyes where the JVN image was gradable, JVN confirmed the presence of an ERM in all 9 eyes (100%). The remaining eye's lesion was within the JVN fields but the quality of the JVN image was compromised by a shadow masking the necessary JVN image, rendering it "ungradable". As per JVN protocol, such a notation would immediately trigger an automatic referral to an ophthalmologist. ETDRS 7-standard field photographs available for this patient confirmed the presence of an ERM. Additional to the 10 eyes reported by the ophthalmologist following DFE, JVN noted one more eye with an ERM. Review of available seven standard field photographs confirmed its presence. Hence, in the 11 eyes in which an ERM was present, JVN images demonstrated and noted 10 (90.9%) while the ophthalmologist also noted 10 (90.9%).

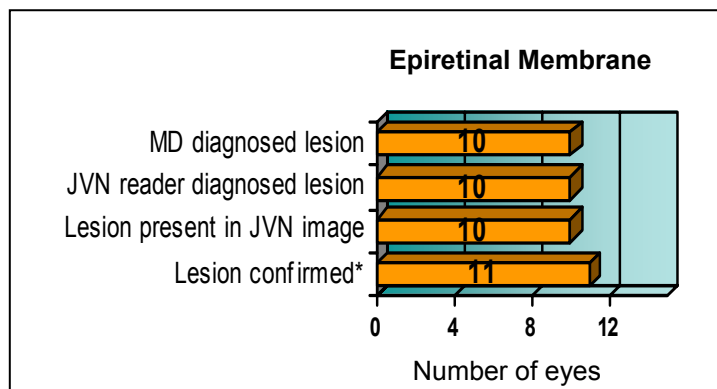


Figure 9: Agreement for epiretinal membrane

Retinal indicators for suspicion of glaucoma

This category encompassed the retinal findings that suggested the need to perform further work-up of the patient for the suspicion of glaucoma. These findings included cup/disc asymmetry of >0.1 , suspicious optic nerve appearance such as questionable thinning or notching of the neural retinal rim, observable nerve fibre layer defects and/or abnormally large cup-to-disc ratio. Non-retinal indicators such as intraocular pressure or family history were not included as criteria since the JVN imaging platform does not currently collect this information.

Of 280 patients, there was exact agreement between DFE and JVN imaging for suspicion of glaucoma in 275 patients (98.2%). Agreement was almost perfect ($\kappa=0.83$). DFE identified 16 patients (5.7%) with at least one positive indicator for suspicion of glaucoma; of these, JVN images demonstrated these retinal findings in all 16 patients (100%) although the JVN reader only noted this in 13 (81.3%). Of the three patients in which the JVN reader did not note these lesions, review of JVN images and seven standard field photographs (available for all three patients) revealed the presence of cup/disc asymmetry. Two of these patients also had sufficient accompanying lesions to trigger further work-up by the ophthalmologist for suspicion of glaucoma. In addition to the 16 patients noted by the ophthalmologist, the JVN reported another two patients with retinal indicators for suspicion of glaucoma. Review of these cases confirmed that these patients did have evident cup/disc asymmetry but no other indicators for glaucoma. These two patients were not noted as “glaucoma suspect(s)” by the ophthalmologist. Hence, of the 18 patients who were confirmed to have at least one positive indicator as “glaucoma suspect”, JVN images demonstrated these

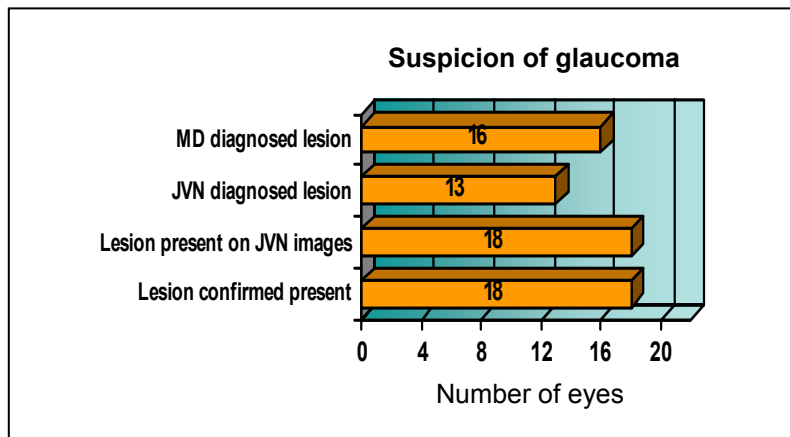


Figure 10: Agreement in identifying suspicion of glaucoma

findings in all 18 (100%) while the JVN reader noted 13 (81.3%) and the ophthalmologist noted 16 (88.9%).

Hypertension, renal disease and/or other systemic risk factors of retinopathy

There was exact agreement between DFE and JVN imaging for the presence of exacerbating systemic conditions in 257 patients' (95.4%) retinopathy. Agreement was almost perfect ($\kappa=0.80$). These systemic conditions included hypertension, renal retinopathy and/or any systemic condition that increases intraocular vascular pressure (eg. Persistent vomiting). Characteristic lesions include multiple soft exudates ("cotton wool spots") of similar appearance and age in close proximity to the optic disc. These differ from diabetes-related soft exudates, which tend to lie further away from the optic disc, differ from each other in age and have associated flame-shaped hemorrhage(s). Arterial attenuation, venous dilation, arterio-venous nicking ("A-V nicking") may also be present, indicating a hypertensive component to the patient's retinopathy.

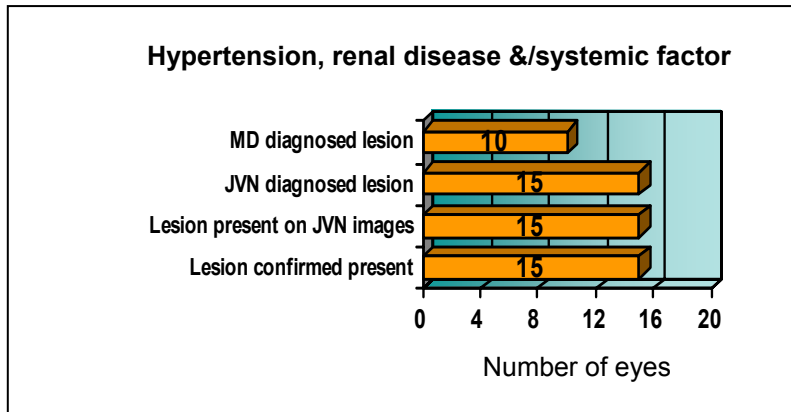


Figure 11: Agreement in presence of systemic risk factors

DFE identified evident bilateral retinopathy with possible systemic components in 10 patients (3.6%) and JVN agreed with all 10 (100%). In addition to these 10 agreements, the JVN further identified another 10 patients with

a possible systemic component to their retinopathy. Of these 10, review of the cases identified 5 (50%) patients in which the JVN reader had over-attributed the soft exudates to a systemic factor when they were diabetes-related. ETDRS 7-standard field photographs were available for all five patients, and confirmed the presence and location of these lesions. The remaining 5 cases in which the JVN noted soft exudates were confirmed on review to be attributable to a systemic factor. These were not noted as such by the ophthalmologist. ETDRS seven standard

photographs available for 4 (80%) of these patients confirmed the presence and location of these lesions, including attenuation of the arterial tree, venous dilation and A-V nicking. Hence, in 15 patients with a possible systemic component, the JVN demonstrated and noted these lesions in all 15 (100%) while the ophthalmologist noted 10 (75%). It is important to note that although the JVN reader over-attributed five diabetes-related soft exudates to a systemic factor, the presence and location of these lesions on JVN images matched those on the ETDRS 7-standard field photographs.

Age-related maculopathy

There was exact agreement between DFE and JVN imaging for the presence or absence of age-related macular degeneration (AMD), macular drusen and/or retinal pigmentary epithelium (RPE) changes in 511 (91.3%) eyes. RPE changes included mottling, RPE dropout or evident atrophy within the macular region. DFE noted the presence of these specific findings in 42 eyes (7.5%); JVN agreed with 30 eyes (71.4%). Of the twelve eyes that disagreed, review of these cases demonstrated the presence of these lesions on JVN images in 9 cases that were not noted by the reader while 3 cases were deemed “ungradable” due to significant cataract (n=2) and a shadow

masking the macular region (n=1).

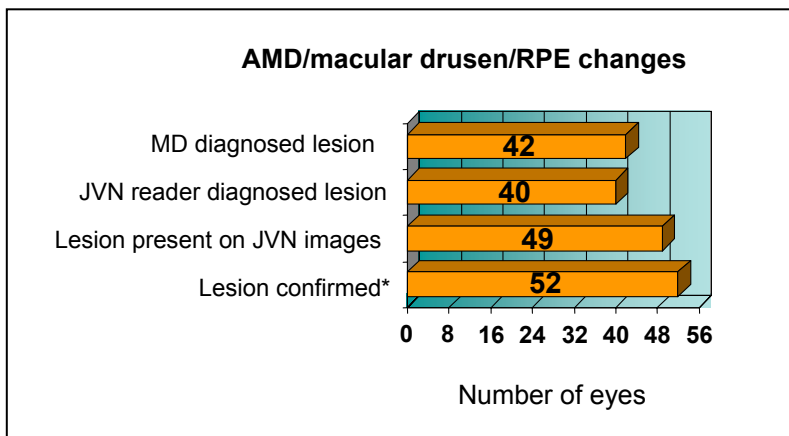


Figure 12: Age-related maculopathy changes

In addition to the 42 eyes noted by the ophthalmologist following DFE to have these changes, the JVN noted 37 other eyes with

findings consistent with AMD, macular drusen and/or RPE changes. Of these 37, the findings ranged from a “single RPE dropout infero-nasal to centre of macula” and “few isolated RPE drop-outs” to “atrophic pigmentary change within macula”. However, the JVN ascribed 54.9% (17/37) of these findings as “mild”. Ten cases were randomly selected from this subset of 37 and reviewed, confirming the presence of the specified lesions on JVN images in all ten cases. None of these were noted by the ophthalmologist. Hence, in the 52 eyes in which lesions indicating AMD, macular drusen and/or RPE changes were confirmed present, the JVN demonstrated 49 cases (94.2%) but noted 40 (76.9%) while the ophthalmologist noted 42 (80.8%). Of all eyes reviewed, agreement was substantial ($\kappa=0.71$).

Cataract and suspicion of cataract

There was exact agreement between DFE and JVN evaluation for the presence and absence of cataract or suspicion of cataract in 534 eyes (95.4%). Presence or suspicion of cataract was based on both JVN retinal images (yellowing and/or haziness of the retinal images) and the external image of each eye, from which the lens' opacity could be discerned. Patients who have had evident corrective cataract surgery were not included as having a diagnosis of “cataract” or “suspicion of cataract” unless there was media opacity post-cataract surgery.

DFE suspected or noted the presence of cataract in 100 eyes (17.9%). JVN images from eleven eyes (1.1%) were not gradable. Of the 89 eyes in which JVN images were gradable, JVN evaluation confirmed the presence or suspicion of cataract in 72 eyes (80.9%). Agreement was almost perfect ($\kappa=0.90$) for all gradable eyes. Of the 15 eyes in which the JVN evaluation did not note or suspect cataract, adjudicator review of JVN images noted “no evidence of cataract in external images and a clear retinal view” in eight eyes and “mild retinal image haziness” in seven

eyes. It is important to note that in all cases where cataract was not detected by the JVN, there was only early cataract (1+ NS) noted during the eye examination by the ophthalmologist. Thus, with cataract analyses repeated for all cases with cataract >1+, JVN identified all cases of cataract that was identified by DFE.

Other ocular conditions noted on JVN evaluation

In addition to the ocular conditions already noted, the DFE also noted the presence of retinitis pigmentosa in one eye, and asteroid hyalosis in one eye. JVN evaluation also identified these findings in the same eye for both cases while noting the absence of these findings in all other eyes. Hence there was exact agreement between DFE and JVN evaluation for the presence and absence of retinitis pigmentosa and asteroid hyalosis in all 560 eyes (100%).

Non-DR ocular finding	JVN cohort Number of eyes=560		Melbourne cohort Number of eyes=279	
	Exact agreement (%)	Kappa value (κ)	Exact agreement (%)	Kappa value (κ)
C-R atrophy and/or scar	100	1.00	99.3	
Retinal emboli	100	1.00	--	--
Retinitis pigmentosa	100	1.00	--	--
Asteroid hyalosis	100	1.00	100	1.00
Epiretinal membrane	99.6	0.90	98.9	N/A*
Suspicion of glaucoma	98.2	0.83	97.1	0.65
Cataract	95.4	0.82	90.0	0.57
Hypertension, renal disease and other systemic risk factors for retinopathy	98.2	0.80	--	--
Choroidal lesion	98.6	0.73	98.2	0.57
AMD, macular drusen and/or RPE changes	91.3	0.71	91.8	0.60
Macular hole	--	--	100	1.00
Bilateral myopic degeneration of the optic disc	--	--	99.3	0.80
CRVO or BRVO	--	--	98.9	0.40

*The Kappa value cannot be calculated for epiretinal membrane in the Melbourne cohort because one variable (non-mydratic digital imaging) remained constant due to not detecting any positive cases.

Table 6: Exact agreement for either presence or absence of non-DR findings within assessed fields, and corresponding Kappa values in all eyes

PART TWO: CENTRE FOR EYE RESEARCH AUSTRALIA (MELBOURNE, AUSTRALIA)

Study Population

OF THE 140 PATIENTS WITH DIABETES MELLITUS (DM) WHO UNDERWENT BOTH NON-MYDRATIC DIGITAL RETINAL IMAGING AND ETDRS 7-STANDARD FIELD PHOTOGRAPHY, 62 (44.3%) WERE FEMALE.

AVERAGE PATIENT AGE AT IMAGING WAS 69.1 ± 9.9 YEARS (RANGE: 34.8 - 90.2 YEARS). AVERAGE DM DURATION WAS 12.6 ± 7.7 YEARS (RANGE: 1.0 TO 39.0 YEARS). AVERAGE AGE AT DIAGNOSIS WAS 55.6 YEARS ± 13.9 YEARS. FOUR PATIENTS (2.9%) WERE DIAGNOSED WITH DM <30 YEARS OF AGE, AGE AT DIAGNOSIS WAS UNKNOWN FOR TWO PATIENTS (1.4%) AND 134 PATIENTS (95.7%) WERE DIAGNOSED AT

≥30 YEARS OF AGE. FOR CONTROL OF DM, 95 PATIENTS (67.5%) WERE USING TABLETS ONLY, 23 PATIENTS (16.4%) WERE USING INSULIN ONLY, 13 PATIENTS (9.3%) WERE USING DIET ONLY AND 9 PATIENTS (6.4%) WERE USING BOTH INSULIN AND TABLETS. ALL DIGITAL IMAGING AND ETDRS PHOTOGRAPHY WERE UNDERTAKEN ON THE SAME DAY IN THIS COHORT.

NON-DIABETES-RELATED FINDINGS

Of 279 eyes from 140 patients, digital images from 260 eyes (93.2%) were gradable for non-DR lesions. Of the 19 eyes with ungradable images, 15 (78.9%) were attributed to cataract and four (21.1%) were due to miotic pupils. Digital images identified 76 patients (54.3%) with at least one non-DR finding. The prevalence of the specific non-DR findings as determined by digital imaging as well as that determined by the ETDRS photographs have been summarized in Tables 5 and 7. Exact agreement and Kappa values for specific lesions have been presented in Table 6.

Central and/or branch retinal vein occlusion

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of retinal vein occlusion in 276 eyes (98.9%). ETDRS photographs identified the presence of a central retinal vein occlusion (CRVO) in two eyes (0.7%) and branch retinal vein occlusion (BRVO) in two eyes (0.7%). Of these, digital image evaluation reported the presence of a CRVO in one eye. Overall, there was fair agreement ($\kappa=0.40$) in determining the presence or absence of retinal vein occlusions.

Chorio-retinal atrophy and/or scar

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of chorio-retinal atrophy and/or scar in 274 eyes (98.2%). ETDRS

photographs identified the presence of a chorio-retinal atrophy and/or scar in four eyes (1.4%). Of these, digital images identified the same finding in two eyes. Of the two cases which were not identified on digital image evaluation, one was noted by the ETDRS photography reader as “small C-R scar”. Overall, there was substantial agreement ($\kappa=0.66$) in detecting C-R atrophy and/or scar.

Non-DR ocular finding	Non-mydrriatic digital images Number of eyes (%)	ETDRS 7-std field photographs Number of eyes (%)
Cataract	40 (14.3%)	36 (12.9%)
AMD, macular drusen and/or RPE changes	24 (8.6%)	39 (14.0%)
Suspicion of glaucoma	4 patients (2.9%)	8 patients (5.7%)
Macular hole	2 (0.7%)	2 (0.7%)
Choroidal lesion	2 (0.7%)	5 (2.5%)
C-R atrophy and/or scar	2 (0.7%)	4 (1.4%)
Bilateral myopic degeneration of the optic disc	2 patients (1.4%)	3 patients (2.1%)
CRVO or BRVO	1 (0.3%)	4 (1.4%)
Asteroid hyalosis	1 (0.4%)	1 (0.4%)
Epiretinal membrane	0 (0%)	3 (1.1%)

Table 7: Prevalence as detected by non-mydrriatic digital imaging and ETDRS 7-std field photography (N=140 patients; n=279 eyes)

Choroidal lesions

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of a choroidal lesion in 274 eyes (97.5%). ETDRS photographs identified the presence of a choroidal nevus in seven eyes (2.5%). Of these, digital images identified two cases. Of the remaining five cases, two were confirmed upon adjudication to be outside the single 45° field encompassed by the digital images. Hence, the overall agreement for choroidal lesions found

within the fields of the digital images was moderate ($\kappa=0.57$). Even when the cases in which the lesion fell outside the single-field but within the ETDRS seven standard fields were included, agreement remained moderate ($\kappa=0.44$).

Retinal indicators for the suspicion of glaucoma

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of retinal indicators for the suspicion of glaucoma in 136 patients (97.1%). Criteria for inclusion into this category have previously been outlined in Part One's results under the same sub-heading as above. ETDRS photographs identified the presence of glaucomatous suspects in eight patients (5.7%). Of these, digital images identified four and cataract prevented evaluation of the optic disc in one patient's digital images. Overall, there was substantial agreement ($\kappa=0.65$) in detecting glaucomatous suspects.

Age-related macular degeneration (AMD) and/or macular drusen

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of AMD and/or macular drusen in 256 eyes (91.8%). ETDRS photographs noted the presence of AMD and/or macular drusen in 39 eyes (14.0%). Of these, digital images identified the same findings in 20 eyes. Of the remaining 19 eyes, six eyes were noted to have cataract and six eyes had findings that were described by the ETDRS photograph reader as "mild drusen", "small drusen" or "hard drusen". Another disagreement arose in one case where a macular hole seen on both ETDRS photographs and digital images was attributed to AMD by the ETDRS photograph reader but not by the digital image reader. Additionally, evaluation of the digital images identified four eyes with positive findings that were not identified by ETDRS photographs. All four cases were noted as "hard drusen" by the digital image reader. Overall, there was moderate agreement ($\kappa=0.59$) in detecting AMD and/or macular drusen.

Cataract and suspicion of cataract

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of cataract in 251 eyes (90.0%). Evaluation of ETDRS photographs including an external view of the eye noted the presence of cataract in 36 eyes (12.9%). Of these, digital images identified the same findings in 24 eyes from evaluation of the retina alone. Criteria for suspicion of cataract include apparent yellowing of the fundus view or otherwise unexplained haziness of digital images. No external view of the eye was available for the digital images. In addition, evaluation of the digital images identified another 16 eyes with cataract although findings in six eyes were noted to be “early cataract” or “slight cataract”. Overall, there was moderate agreement ($\kappa=0.57$) in detecting cataract.

Epiretinal membrane

There was exact agreement between evaluation of digital images and ETDRS photographs for the presence or absence of epiretinal membrane in 275 eyes (98.6%). ETDRS photographs identified the presence of an epiretinal membrane (ERM) in three eyes (1.1%). Of these, ungradable digital images prevented the detection of ERM in one case. Digital images did not correctly identify ERM in the other two cases although a query of “retinal pathology – unknown origin” was raised in one case. Kappa values could not be calculated as the digital image evaluation did not demonstrate a positive finding.

Other ocular findings noted on evaluation of non-mydriatic digital images

In addition to the ocular conditions already noted, evaluation of the digital images also found macular hole in two eyes, asteroid hyalosis in one eye and bilateral myopic degeneration of the disc in three patients. Exact agreement between digital images and ETDRS photographs for both

macular hole and asteroid hyalosis was 100% with perfect agreement ($\kappa=1.0$) in identifying the positive cases. Bilateral myopic degeneration of the disc was identified by ETDRS photographs in three patients (2.1%). Digital images matched this identification in two cases. Exact agreement for presence or absence of this finding was thus 99.3% with substantial agreement ($\kappa=0.80$).

DISCUSSION

DIABETES-RELATED FINDINGS

Prevalence of Diabetic Retinopathy

In the Joslin cohort, the JVN identified 53.8% (301/560) of eyes with presence of DR. This is similar to another clinic-based JVN study at the Joslin Diabetes Center in Boston, USA where JVN evaluation identified presence of DR in 56.7% (595/1049) of eyes.^{lxxxiii} In a JVN study of participants in the Joslin Diabetes Center's DO IT (Diabetes Outpatients Intensive Treatment) program, 66.5% (356/535) of eyes had some degree of DR. This is not surprising considering the nature of the DO IT program where people whose diabetes is increasingly refractory to self-management undertake a 3.5-day program incorporating comprehensive diabetes counseling, medical evaluation and diabetes education with a multi-disciplinary team of an endocrinologist, nurse educator, dietician and exercise physiologist.² However, the prevalence of DR in this study is higher than that found in the JVN study involving 1720 patients at the Togus Veterans Administration Medical Center (VAMC) in Maine, USA where 40.5% (697/1720) of patients had presence of DR.^{lxxxiv} Differences in prevalence could be due to the shorter duration of diagnosed DM in the Togus cohort (7.6 years) compared to this study's Joslin cohort (10.8 years) as DM duration has been demonstrated as an independent risk factor for retinopathy in several studies.^{lxxxv,lxxxvi} The higher prevalence at Joslin is may also be explained by a sampling bias since the nature of Joslin is a specialist high-volume institution solely dedicated to patients with diabetes.

The prevalence rates of the above clinic-based cohorts are higher than population-based studies where DR affects 33.8% (5.3 million) of the 15.7 million people with diabetes ≥ 18 years of age in the USA.^{lxxxvii} This difference between clinic-based and population-based studies have also been

shown in Australia, where the population-based AusDiab study involving 11,247 adults with diabetes ≥ 25 years of age reported a prevalence rate of 24.5% in those with known diabetes³⁷ compared to the clinic-based Newcastle DR study over 11 years (1977 to 1988) with prevalence rates of 35%.^{lxxxviii}

Prevalence rate for DR as determined by dilated fundus examination by a retinal specialist (49.6%) slightly differed from that determined by the JVN (53.8%). Interestingly, a difference of similar magnitude and direction was also reported by Moss et al.^{lxxxix} when comparing dilated ophthalmoscopy (44.9%) and mydriatic 7-standard field fundus photography (52.0%) in 1949 participants from the population-based WESDR cohort.

Ungradable images

In this study, JVN images from 9.8% (55/560) of eyes were deemed not gradable for DR primarily due to cataract (25/55; 45.5%). Heaven et al.^{xc} and Taylor et al.^{xcii} in the UK as well as Harper et al.³⁶ implementing a DR evaluation program in rural Victoria, Australia reported similar findings in the use of their non-mydriatic retinal camera at 9.5% (86/912), 10.0% (433/4312) and 9.3% (217/2354) respectively. Klein et al.^{xcii} also reported similar results in a comparison of a non-mydriatic camera and a standard fundus camera, with ungradable photographs from 12.7% (8/63) of patients taken through an undilated pupil. The Digital Diabetic Screening Study^{xciii} reported slightly lower numbers, with images from 8.1% of patients (16/197) deemed not gradable. This is likely due to the fact that the majority of DR severity in their study was concentrated in the lower DR levels (194/197; 98.5%) and the proportion of ungradable digital images has been reported to increase with DR severity.^{xciv}

Comparison of JVN evaluation and dilated fundus examination for DR

In this study, JVN evaluation for level of DR severity agreed exactly or within one level of retinopathy with clinical examination by the retinal specialist in 97.0% (490/505) of gradable eyes. This was almost identical to a previous study comparing JVN with clinical examination for DR evaluation in the Joslin Diabetes Center's DO IT patient cohort where exact agreement or agreement within one level of retinopathy was 96.7% (478/494) of gradable eyes. Results were still similar between this study (87.5%; 490/560) and the DO IT study (89.3%; 478/525) when eyes with ungradable JVN images were included in the analysis.

A comparison study between digital imaging and clinical examination by ophthalmologists by the Diabetic Digital Screening Group⁹⁶ identified an almost identical level of exact agreement (75.0%) with this study (75.5%). However, their study was skewed towards the lower levels of DR severity with only 1.5% (3/197) of their patient cohort diagnosed with severe NPDR and PDR compared with 13.2% (37/280) of our patient cohort and ophthalmoscopy has been noted to have poorer sensitivity in detecting early stages of DR.^{xcv,xcvi,xcvii} Olson et al.^{xcviii} also report similar findings in the UK when comparing high-resolution two-field 50° digital photography versus slit-lamp biomicroscopy by ophthalmologists with exact agreement in 80.4% (442/550) of participants. However, their imaging protocol required pharmacological pupil dilation and the two-field EURODIAB grading protocol with five clinical levels of DR severity were used instead of the seven-level ETDRS extension of the modified Airlie House classification that was used in this present JVN study. Their technology specifications also differed with higher resolution (1024x1024) and slightly wider retinal fields (50°) compared to this present study (640x480 and 45° respectively).

Other studies have compared retinal imaging with clinical examination for DR evaluation but many differed in their imaging and grading criteria, whether it was in terms of pupil dilation, number of retinal fields imaged or digital and telemedicine capability even without consideration of differing patient demographics. Clinical examination used as comparison also differed in modality (slit-lamp biomicroscopy, direct or indirect ophthalmoscopy) and qualifications of the examiner (ophthalmologist, optometrist, primary care physician or nurse). Only the studies with ophthalmologists performing the clinical examination were considered for comparison in this discussion.

This present study utilized the seven-level ETDRS extension of the modified Airlie House classification to determine DR severity yet its level of exact agreement (75.5%) is remarkably similar to other studies that used a less stringent definition such as “presence of any retinopathy” or a “referral threshold” in detecting DR to calculate exact agreement. For example, Mohan et al.^{xcix} in the UK compared direct ophthalmoscopy with non-mydriatic single-field 45⁰ retinal imaging in a high-volume diabetic clinic in determining presence or absence of DR and found exact agreement in 72% (119/165) of eyes. Taylor et al.⁹⁴ compared dilated ophthalmoscopy versus non-mydriatic fundus photography for presence or absence of DR in 4312 eyes. Overall agreement was not presented in that paper but later calculated by Lee et al.^c to be 76.8%. Scanlon et al.^{ci} compared digital non-mydriatic single-field 45⁰ images with slit-lamp biomicroscopy for “referable DR” (defined as moderate or worse NPDR, any PDR and/or maculopathy) and found agreement in 60.1% (927/1542) of patients. A study of 410 Oklahoma Indians (795 eyes) reported a high agreement (86.3%) in comparing 45⁰ retinal photography with a non-mydriatic retinal camera versus slit-lamp biomicroscopy and indirect ophthalmoscopy by retinal specialists.¹⁰³ However, their study used a three-level DR severity grading protocol (No DR, NPDR and PDR) and despite

using a non-mydratic camera, pharmacological pupil dilation was undertaken. Klein et al.⁹⁸ also found that mydriasis when using a non-mydratic camera increased agreement from 82.5% (63/99) to 86.5% (74/99) of patients. In the same study, exact agreement between direct ophthalmoscopy and mydratic 30° fundus photography was 54.3% using three levels of DR severity (no DR, NPDR and PDR). The authors conclude that “if the pupil is not to be dilated, then non-mydratic camera may offer a more sensitive and objective method of detecting DR than direct ophthalmoscopy”.

Moss et al.¹⁰⁰ compared ophthalmoscopy and mydratic stereoscopic 7-standard field fundus photography in the WESDR cohort and reported overall agreement in determining three broad levels of DR severity (no DR, NPDR or PDR) at 85.7%. Considering that the latter modality is considered the gold standard for evaluating DR²⁵ and that broader categories of DR were used by Moss et al., the level of agreement found in this present study (87.5% within one level of DR severity in all eyes) was indeed excellent. This is not surprising as Bursell et al.¹ had previously identified substantial agreement between the JVN and mydratic stereoscopic 7-standard field fundus photography; other studies comparing digital retinal imaging and slide films also demonstrated this similarity.^{cii,ciii} Overall, this study has once again demonstrated that the JVN is an excellent platform for evaluating severity of diabetic eye disease.

Macular edema

JVN evaluation identified 59 eyes (10.5%) with presence of diabetic macular edema (DME). This is comparable to that found in the JVN cohort of the DO IT Study where diabetic macular edema were identified in 9.1% (95/1049) eyes. This is also comparable to another tele-ophthalmology study where 9.9% (12/121) of patients were diagnosed with macular edema.¹⁰⁶

In this study, there was exact agreement for CSME in 78.4% (439/560) of total eyes and in 92.4% (439/560) of eyes with gradable images. 15.2% (85/560) of macular images were not gradable for macular edema. This is similar to the study involving 207 eyes by Rudnisky et al.^{civ} who reported exact agreement in 83.6% for CSME, but their imaging protocol required pharmacological pupil dilation and utilized a high-resolution (3040x2008 pixels) digital stereoscopic 30° of the macula with contact lens biomicroscopy by a retinal specialist as the reference standard. Unlike this present study, presence of cataract or media opacity was an exclusion criteria for their study but they still had a greater proportion of ungradable images (16.8%) compared to this study (15.2%).

NON-DIABETES-RELATED OCULAR FINDINGS

Prevalence of non-DR findings in two populations

In this study, non-DR findings were found in a significant number of patients in both the Joslin and Melbourne cohorts. 40.7% (114/280) of patients in the Joslin cohort having at least one non-DR finding. This is similarly high in another clinic-based JVN study at Joslin Diabetes Center where non-DR findings were identified in 39.5% (414/1059) of eyes.⁸⁶ In the Melbourne cohort, 54.3% (76/140) of patients had at least one non-DR finding. The higher prevalence could be due to differences in age (Joslin, 50.0 ± 14.9 years; Melbourne, 69.1 ± 9.9 years) as prevalence of vision impairment has been shown to increase threefold with each decade after the age of 40, with almost one in three people over the age of 80 having impaired vision.^{cv} Cavallerano et al. also noted that 25.9% (136/525) of patients in the JVN study of the DO IT cohort had non-DR findings requiring referral for evaluation; of these, 61.8% (84/136) would not have been referred for clinical examination based on clinical level of DR or diabetic macular edema alone.²

Not surprisingly, the prevalence rates for non-DR findings in the previous four clinic-based JVN and Melbourne studies were significantly higher than that in a community-based study in rural Victoria, Australia where 9% (101/1177) of people being evaluated for DR had evidence of fundus pathology other than DR.^{cvi} The majority of these were age-related maculopathy, retinal vascular occlusions and pathological optic disc cupping suggesting glaucoma. Other recent studies in Mississippi, USA and Canada have also started to incorporate assessment of non-DR findings into their DR evaluation programs. Rudnisky et al.³⁶ in a province-wide tele-ophthalmology program characterizing 540 First Nations people with diabetes noted that only 36.6% (37/101) of the people referred for further evaluation were for treatable DR. The remaining 63.4% (64/101) of referrals were for non-DR findings of cataract, suspicion of glaucoma, retinal vein occlusions, age-related maculopathy and inadequate digital images. In a study based at a Veterans Affairs diabetic eye clinic in Mississippi, USA, non-DR findings such as suspicion of glaucoma, cataract, epiretinal membrane, presumed histoplasmosis and large chorio-retinal scars were detected in 16.9% (209/1236) of eyes.^{cvi}

Also, it is important to note that in this study, 22.8% (59/259) of the Joslin patients *with no DR* had at least one non-DR finding warranting referral for a comprehensive eye examination. Aiello et al.⁸⁶ reported similar findings in their clinic-based JVN study, with non-DR findings identified in 34.8% (158/454) of patients with no DR. These findings were lower than that found in the Togus JVN cohort where 58.3% (596/1023) of patients with no DR had at least one referable non-DR findings.⁷¹ This could be due to the older age of the Togus JVN cohort (63.2 years) compared to the Joslin JVN cohort (50.0 years). These findings emphasize the importance of retinal evaluation for people with diabetes, regardless of DR severity.

Comparison of JVN/non-mydriatic digital retinal imaging and dilated fundus examination for non-DR findings

When lesions were present within retinal fields imaged by JVN, the JVN showed almost perfect agreement beyond chance ($\kappa \geq 0.80$) with clinical examination for most non-DR lesions with substantial agreement for AMD and/or macular drusen ($\kappa=0.71$) and choroidal lesions ($\kappa=0.73$). In the Melbourne cohort, there was moderate to substantial agreement ($\kappa=0.40 - 0.79$) between non-mydriatic digital retinal imaging and ETDRS 7-standard field photography for most non-DR findings with almost perfect agreement ($\kappa=0.80$) for myopic degeneration of the disc. Differences in the Kappa values between these two cohorts must be interpreted with caution for the following reasons: Firstly, this current study was designed as two separate smaller studies with different and distinct patient cohorts and study protocols hence results should primarily be interpreted as such. Secondly, it is important to note that the two imaging systems differ in their intended purpose and approach. The JVN platform is a telemedicine initiative that aims to not only facilitate access of people with diabetes into regular eye or health care programs but also to appropriately triage and prioritize care of patients in high-volume environments by rapidly and correctly identifying those in need of the most urgent care. Hence there is a need for highly accurate evaluation modality comparable to current gold-standards in clinical care.^{cvi} This differs from the approach of the Melbourne study, which aims to evaluate the potential of digital retinal images without pupil dilation as a screening tool to ensure that ocular pathology that is not necessarily DR can be identified in people with diabetes. This difference is evident through the differing imaging protocols where the JVN platform captures non-simultaneous stereoscopic three-field 45° colour images while the Melbourne study captures non-stereoscopic single-field 45° colour images. Both platforms do, however, utilize digital technology and do not require mydriasis. Differences in imaging protocol can also explain the differences in agreement as measured by Kappa. Thirdly, the Melbourne

cohort was half the size of the Joslin cohort and hence the resulting small number of positive cases is a limitation of the Melbourne study.

The implication of having a small number of positive cases should also be considered when noting the perfect agreement ($\kappa=1$) for detecting retinal emboli, retinitis pigmentosa and asteroid hyalosis in the Joslin cohort with asteroid hyalosis and macular hole yielding perfect agreement in the Melbourne cohort. However, the perfect agreement in identifying urgent medical and ocular conditions such as retinal emboli and macular hole is promising and this important finding should be emphasized.

Limitations in detecting non-DR findings

One of the major concerns about non-mydriatic photography has been that important lesions may lie outside the 45° field examined and hence be missed.^{cix} The main limitation in detecting non-DR was the indeed the location of non-DR findings outside standard JVN fields. For example, when the lesion was present within the JVN-evaluated fields, there was also perfect agreement ($\kappa=1$) in the Joslin cohort for detecting C-R atrophy and/or scar. However, when all C-R atrophy and/or scars detected by DFE were included in the data analysis including two lesions outside both JVN-evaluated fields and available ETDRS 7-standard field photographs, agreement decreased slightly to “almost perfect” ($\kappa=0.86$). This is similarly the case for choroidal lesions, where 35.7% (10/28) of lesions present were detected by DFE to be outside JVN-evaluated fields. Review of available ETDRS 7-standard field photographs confirmed that 33.3% (2/6) of these lesions were within the ETDRS 7-standard fields but not JVN fields while the remaining 66.7% (4/6) of cases were outside both JVN and ETDRS 7-standard fields. Agreement for choroidal lesions within JVN fields was substantial ($\kappa=0.73$) with a corresponding decrease to moderate agreement ($\kappa=0.55$) when lesions

outside JVN-evaluated fields were also included. Agreement for choroidal lesions in the Melbourne cohort remained moderate despite decreasing slightly from $\kappa=0.57$ to $\kappa=0.44$ when the two lesions outside the single-field were included.

Dilated fundus examination also identified other clinically significant lesions outside JVN-evaluated fields in eight eyes (1.4%). These included peripheral lattice degeneration (n=3), peripheral retinal hole (n=2) and iris rubeosis (n=3). It has been previously noted that iris rubeosis may not necessarily be detected using mydriatic retinal photography.^{cx} Mohan et al.¹⁰² found that 3.5% of diabetic lesions were detected outside the non-mydriatic single-field in one UK study and Klein et al. have suggested that retinopathy may lie outside the single-field in 8-15% of cases.⁹⁸ Ability to detect non-DR findings may improve with modification of imaging techniques, including possibly expanding JVN fields to encompass more retina for evaluation.

Detection of lesions by the JVN/non-mydriatic digital retinal imaging when the dilated fundus examination did not

It is interesting to note that the JVN accurately detected lesions not noted by the retinal specialist following DFE in five of the seven non-DR lesion types where there was disagreement. These lesions were clearly evident on review of JVN images by an independent senior retinal specialist (L.M.A.) and confirmed by available ETDRS 7-standard field photographs, yet were not noted by the retinal specialist. For example, JVN alone identified 38.9% (7/18) of all choroidal lesions within JVN fields; 33.3% (5/15) of all cases of hypertension, renal disease and other systemic risk factors for retinopathy; 20.4% (10/49) of all AMD, macular drusen and/or RPE changes; 11.1% (2/18) of all patients with suspicion of glaucoma and 9.1% (1/9) of all cases of epiretinal membrane. Cataract

and C-R atrophy and/or scar were the only non-DR lesion types in which the JVN did not detect any new lesions previously undiagnosed by the retinal specialist.

Possible explanations for this include firstly considering the limitations inherent in any retrospective chart review. For example, following examination of a patient, the retinal specialist may only document findings that they deem “clinically significant” rather than every visible lesion as the JVN reader is trained to do. Implementing well-defined criteria for grading non-DR findings and standardizing these between the JVN reader and the retinal specialist may also improve agreement. For example, what the retinal specialist may note as “macular drusen” were sometimes noted by the JVN reader as “AMD” (unpublished data). In this study, we pooled both AMD and macular drusen findings to account for this but additional prospective studies need to ensure that well-defined criteria are implemented for detecting lesions. This contrasts with the grading of DR where the ETDRS extension of the modified Airlie House classification is used by both the retinal specialist and JVN reader.

Secondly, there is also the likelihood that JVN imaging has advantages in its image acquisition, grading and archiving capabilities over a dilated fundus examination. These include having a longer duration of time in assessment of the retinal image than may be feasible during a routine eye examination within a busy high-volume environment, which may partly account for the closer agreement between JVN imaging and ETDRS 7-standard field photography than between clinical examination and ETDRS 7-standard field photography in this study. JVN retinal images are also advantageous in their ability to provide objective documentation of a patient’s ocular health status at a point in time; this is analogous to the use of ETDRS 7-standard field photographs to provide baseline or further documentation as per current practice at the Beetham Eye Institute of Joslin

Diabetes Center. The importance of having objective documentation of patients has also been noted in other epidemiologic studies and clinical trials.¹⁰⁰ Although the clinical use of ETDRS 7-field photography is not commonplace due to practical considerations, it still remains the gold standard for evaluating diabetes-related ocular findings in terms of sensitivity and specificity.²⁵ In view of these findings and the previous JVN validation study by Bursell et al.¹ where the JVN was in substantial agreement ($\kappa=0.65$) with ETDRS 7-standard field photography for clinical levels of DR, it is clear that the JVN has enormous potential to help address and improve eye health care for the community.

However, it must be noted that the integrity of the JVN clinical pathway is dependent on the training and continuous updating of skills for the JVN readers. As found in this study, most lesions present on ETDRS 7-standard field photographs were also present in the JVN images. (Figures 7 to 12) However, the JVN reader may not note this in their diagnosis template. Hence training JVN readers concentrate on *detection* of specific lesions rather than *diagnosis* of conditions, such as noting macular drusen and RPE changes rather than categorically diagnosing AMD. (Personal communication, Paula Katalinic, 2003) Non-DR findings trigger a referral for a comprehensive eye examination, which will then perform further work-up of that patient's eye health. The ability of the JVN to appropriately triage and prioritize patients in terms of their urgency to seek eye health care ensures that not only *more* people access eye examinations but that those in most need are addressed first. The JVN is not intended to replace a comprehensive eye examination, but to facilitate access and improve the standard of eye health care in the community with special attention to people currently receiving sub-optimal eye health care.

Previous initiatives have attempted to address this disparity through the use of non-mydratric retinal cameras, mobile retinal units, outreach visits by ophthalmologists into under-served communities in both rural and urban areas with accompanying public health strategies. The difficulty lies not only in improving access to eye examinations, but also in ensuring that the patients are motivated to actively engaged in a life-long program of improved eye health care. Hence it is important that any eye health care program implemented is perceived to be sustainable and acceptable by the community. The JVN platform offers this by addressing both potential barriers perceived by patients such as reluctance to undergo mydriasis as well as healthcare delivery issues such as ensuring that a permanent support system is constantly available through affiliation with tertiary healthcare institutions. There is also the added advantage of the JVN being able to be adapted to be culturally sensitive to the population it is serving, such as training local residents to acquire the JVN images.

CONCLUSION

Overall, this study has demonstrated the potential of the JVN to provide eye evaluation for disorders other than diabetic retinopathy. Further improvement in digital image resolution and imaging techniques may further increase level of agreement.

In addition, the large number of diabetic patients with non-DR findings and no DR (22.8%) reinforces the importance of retinal evaluation in all people with diabetes, regardless of extent of retinopathy. Additional prospective studies are justified to validate the ability of the JVN to diagnose and appropriately triage care of non-DR ocular disorders. This will ensure that eye health care within the Joslin Diabetes Eye Health Care model utilizing the JVN telemedicine

platform will be better tailored to an individual's ocular and medical needs rather than merely by DR severity.

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