Telemedicine and Diabetic Retinopathy

Moving Beyond Retinal Screening

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Current projections estimate that diabetes mellitus will afflict over 439 million individuals worldwide by 2030. The task of detecting and evaluating for the presence and severity of retinopathy in the populations with diabetes mellitus is enormous. Although current methods of treatment are effective in reducing the risk for vision loss, a substantial proportion of patients still do not receive appropriate eye care. The use of an ocular telemedicine–based approach has the potential to expand the reach of these highly effective treatments to virtually any location. Novel methods of image acquisition and analysis, as well as the identification of predictive biomarkers, will need to be developed to further enhance this approach of eye care delivery. In addition, such programs will allow the rapid transfer of clinically relevant discoveries and will allow a considerably larger benefit to a broader patient population.

Diabetic retinopathy (DR) affects nearly half of the population with diabetes mellitus (DM) and remains a leading cause of vision loss. The global prevalence of DM has been continually increasing, and current projections estimate that 439 million adults will be affected by 2030. Given this estimate, a minimum of 2.4 million eyes would need to be evaluated for retinopathy every day. The task of detecting and evaluating retinopathy in populations with DM is enormous and will cause considerable economic and resource burden to health care systems worldwide. Ocular telemedicine programs with a variety of technical enhancements and identification of new predictive biomarkers may hold the potential to address this need.

CURRENT LEVELS OF CARE

From 2009 to 2034, the number of people in the United States with DM will increase from 23.7 million to 44.1 million, with an associated increase in DM-related health expenditures (from $45 billion to $171 billion). The projected increase in the population with DM is even more pronounced from a global perspective. The estimated prevalence of DM worldwide will increase from 6.4% in 2010 to 7.7% in 2030, representing an additional 154 million cases. Over this time period, there will be a 69% increase in the numbers of adults with DM in developing countries and a 20% increase in developed countries. This public health burden is further magnified by the projected disproportionately low 2% per year growth rate for the number of ophthalmologists, almost inevitably leading to a shortage of appropriate eye care.

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be absent in some locations. Present global estimates for access to appropriate DM eye care among developed countries range from 60% to 70%, with significantly lower rates in less developed countries. With an expected 54% increase in the global population with DM, this discrepancy in DM eye care will be further magnified, making it unlikely that simple expansion of current eye care coverage will suffice. Methods to distribute quality eye care to virtually any location at minimal cost must be developed and sustained. Barriers to DM eye care not only involve physical limitations of the health care system but also economic, social, and educational aspects. Incorporation of approaches that improve public awareness, patient and health care provider education, community outreach, and cultural sensitivity will need to be integrated into telemedicine-based programs of comprehensive DM care.

**IMPORTANCE OF DETERMINING RETINOPTHAPY SEVERITY**

Early detection, accurate evaluation, timely treatment, and careful follow-up have been established by multiple large randomized control trials to greatly reduce the risk for vision loss among patients with DM. At the minimum, a yearly retinal evaluation is required for patients with both type 1 and type 2 DM. A more frequent examination interval is required for patients with advancing disease severity. The foundation of effective DM eye care relies on the accurate identification and appropriate determination of the DR severity, routine life-long eye care, coordinated medical care, and prompt treatment when indicated. The mainstay of treatment of proliferative DR (PDR) is panretinal photocoagulation, which has been shown to reduce the risk of severe vision loss to less than 4%. Panretinal laser photocoagulation has been shown to induce sustained regression and prevent vision loss from diabetic retinopathy. The threshold for treatment and the frequency of follow-up intervals is based on progression rates to PDR and projected rates for severe vision loss. It is essential that an ocular telemedicine program for DM eye care accurately detects and determines DR severity in order to recommend appropriate evidence-based medical and eye care.

**THE TELEMEDICINE APPROACH: EXPANDING THE BOUNDARIES OF EVIDENCE-BASED DM EYE CARE**

An ocular telemedicine-based approach to address the need for detecting and determining diabetic retinopathy severity expands our standard concept of eye care delivery. Through telemedicine, the physician's examination room is brought to the patient within a culturally adaptable context at little additional or no cost to the patient. This system provides the additional benefits of greater flexibility in timing, avoiding pupil dilation and the potential to be combined as a targeted patient educational encounter. Furthermore, the broad reach of telemedicine may facilitate clinical trial participation as well as disseminate clinically relevant advancements more rapidly.

The development and implementation of an effective telemedicine program involves adequate quality assurance, cost containment, efficient patient and health care provider workflow, adequate reimbursement for sustainability, and compliance with regulatory requirements. As with all scientific innovations, rigorous validation of these clinical programs must be conducted to ensure that the new programs match or exceed the standard of care. The American Telemedicine Association (ATA) published position statements to provide standards and guidelines for telemedicine programs for DR. Early Treatment Diabetic Retinopathy Study (ETDRS) 30°, 7 standard field color slides (ETDRS photographs) have been chosen as the reference for validating retinal images acquired by ocular telemedicine programs for DR. To ensure accuracy and validity of a telemedicine program for DR, the interpretation of images acquired should compare favorably with ETDRS photography in terms of k values for agreement, false-positive and false-negative values, and positive and negative predictive values. Furthermore, to clarify patient and provider expectations for such programs, the ATA developed telehealth practice recommendations for DR and described 4 categories of clinical validation of a DR telemedicine program. Category 1 validation identifies patients who have no or minimal DR and those who have more than minimal DR. Category 2 validation identifies patients who do not seem to have sight-threatening DR and those who have potentially sight-threatening DR and require prompt referral and possible laser surgery (severe nonproliferative DR [NPDR] or worse). Category 3 validation allows patient treatment to match clinical recommendations based on clinical retinal examination through dilated pupils. Category 4 validation indicates that a program can replace ETDRS photographs in any clinical or research program. Currently, there are no programs with category 4 validation, and establishing such a program remains a goal that has the potential to significantly improve the level of DM eye care and change the way diabetic eye disease is diagnosed and monitored.

**A TELEMEDICINE APPROACH: EXPERIENCE WITH 1 SYSTEM**

There are several telemedicine approaches currently addressing the issue of diabetic retinopathy. Herein, we discuss one such validated system with extensive usage and evaluation. The Joslin Vision Network Diabetes Eye Care Program (JVN) is the telemedicine program of the Joslin Diabetes Center, Boston, Massachusetts. Conceived, designed, validated, and deployed through the Beetham Eye Institute (BEI) of the Joslin Diabetes Center, the JVN follows strict protocols for acquiring pertinent patient history, acquiring retinal images, grading level of DR, and reporting findings and treatment guidance plans to patients and their health care providers (Figure 1). Certification programs and ongoing quality...
monitoring ensure that all JVN imagers, graders/readers, and patient care coordinators adhere to the established, validated protocols.

**JVN Validation**

The JVN has been validated to provide ATA category 3 DM eye care through well designed and executed prospective and retrospective studies. In a prospective study of 54 patients (108 eyes) comparing nonmydriatic JVN images to ETDRS photographs, there was substantial agreement ($\kappa = 0.65$) between the clinical level of DR assessed from the undilated JVN images and the dilated ETDRS photographs. Agreement was excellent ($\kappa = 0.87$) for recommended referral to ophthalmology specialists for eye examinations. Comparison of individual lesions between the JVN images and the ETDRS photographs for interreader comparisons were comparable with those from the prior ETDRS study.\(^{13}\)

In a retrospective study of 268 patients who had comprehensive eye examination by a retinal specialist at the BEI following JVN imaging, JVN diagnosis of a clinical level of DR agreed exactly with clinical findings in 388 eyes (72.5%) or within 1 level in 478 eyes (89.3%). The JVN referral based on the more severe diagnosis in either eye matched retinal specialist–recommended follow-up in 248 of 268 of patients (92.5%). A total of 136 of 525 of JVN patients (25.9%) had nondiabetic ocular abnormalities requiring referral.\(^{14}\)

A prospective study of 52 patients documented as having no or mild NPDR (ETDRS level ≤35) and no diabetic macular edema (DME) at dilated retinal examination 11 or more months earlier compared level of DR determined from JVN images, clinical examination, and ETDRS photographs. In the 102 gradable eyes (98.1%), JVN diagnosis exactly matched clinical examination for level of DR in 82 eyes (77.9%) and was within 1 level of DR in all eyes (100%). Three eyes (2.9%) had JVN images ungradable for DME, 1 of which had DME by clinical examination. The JVN diagnosis matched clinical examination for DME in all 101 eyes gradable by JVN. In a satisfaction survey following JVN imaging and examination, 50 patients (96.1%) reported that JVN imaging improved their understanding of eye disease; 100% were satisfied with JVN, and 48 (92.3%) would consider replacing dilated examination by their eye physician with JVN imaging.\(^{15}\)

In a retrospective study reviewing the medical records of 244 patients with DM who had a dilated fundus examination and JVN imaging performed within 1 year of each other at 4 US Department of Defense locations in the metropolitan Washington, DC, area, there was 86% agreement in the grading between JVN images and dilated fundus examination in images of 311 gradable eyes. The overall sensitivity of gradable JVN images was 98%, and the specificity was 100% for retinopathy within 1 grade of the DFE.\(^{16}\)

In a retrospective medical chart review of 280 BEI outpatients (560 eyes) with type 1 or type 2 DM comparing findings of non–DM-related eye disorders from JVN digital images with findings from dilated retinal examination by retinal specialists, JVN imaging identified at least 1 non–DM-related finding in 114 of patients (40.7%). Non-DM ocular pathologic features identified by digital images, clinical examination, or both included cataract (100 eyes [17.8%]); age-related maculopathy (52 eyes [9.3%]); suspicion of glaucoma (18 eyes [3.2%]); choroidal lesions (18 eyes [3.2%]); evidence of systemic disorder (eg, hypertension or renal disease; 15 patients [5.4%]); epiretinal membrane (11 eyes [2.0%]); chorioretinal atrophy, scar, or both (6 eyes [1.1%]); retinal emboli (3 eyes [0.5%]); retinitis pigmentosa (1 patient [0.2%]); and asteroid hyalosis (1 eye [0.2%]). Agreement of nonmydriatic imaging with clinical examination for presence and absence of these findings was 95.4%, 91.3%, 98.2%, 98.6%, 98.2%, 99.6%, 100%, 100%, 100%, and 100%, respectively. The $\kappa$ values for all non-DR lesions demonstrated near–perfect agreement ($\kappa \geq 0.80$) except for age-related maculopathy ($\kappa = 0.71$) and choroidal lesions ($\kappa = 0.73$), where agreement was substantial.\(^{17}\)

**JVN Clinical Programs**

The JVN is most effective when deployed in nonophthalmic environments. Clinical deployment of JVN programs has resulted in improved clinical outcomes. In the Indian Health Service, addition of a JVN program increased the rate of examination and treatment for DR. In a defined population of patients with DM at the Phoenix (Arizona) Indian Medical Center, implementing a JVN program in a primary care setting resulted in a notable increase in the rate of DR surveillance and a proportional increase in the rate of laser treatment for DR for a large patient population. The rate of annual retinal examinations increased from 30% (95% confidence interval of 20% to 40%) to 65% (95% confidence interval of 60% to 70%) after a JVN program was implemented.\(^{18}\)

**Figure 1.** Images of the left eye showing fields covered by Early Treatment Diabetic Retinopathy Study (ETS) photographs (A) and Joslin Vision Network Diabetes Eye Care Program (JVN) images (B). For the JVN images, a total of 22 nonmydriatic retinal images are taken for each eye. The retinal images include 3 nonsimultaneous stereoscopic 45°-field and 2 nonsimultaneous stereoscopic 30°-field nonmydriatic digital images. Early Treatment Diabetic Retinopathy field 1 (F1), field 2 (F2), and field 7 (F7); Joslin Vision Network Nonmydriatic field 1 (NM-1), field 2 (NM-2), and field 3 (NM-3).

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interval [CI], 44%-56%) to 75% (95% CI, 70%-80%; P < .001), representing a 50% increase in the retinal examination rate. The rate of laser therapy increased from 19.6 per 1000 patients with DM in 1999 to 29.5 per 1000 in 2003 for a 51% increase in the laser treatment rate.18

In a retrospective observational cohort study,19 1219 patients (2437 eyes) with DM, impaired fasting glucose, or impaired glucose tolerance at the Togus, Maine, VA Medical Center underwent JVN protocol imaging: 1536 eyes (63.0%) had no DR, 389 eyes (16.0%) had mild NPDR, 105 (4.3%) had moderate NPDR, 35 (1.4%) had severe NPDR, 20 (0.8%) had very severe NPDR, 32 (1.3%) had PDR, and 320 (13.1%) were ungradable. Regarding DME, 1907 eyes (78.3%) had no DME, 34 eyes (1.4%) had early DME, 16 (0.7%) had clinically significant macular edema (CSME), and 480 (19.7%) were ungradable for DME. Of all patients, 354 (29.0%) had either no DR or mild NPDR in both eyes, no evidence of DME, and no clinically significant non-DM findings. A total of 679 (35.7%) had no DR in either eye, and 229 (18.8%) had mild NPDR in the more severe eye. Of the 908 patients with either no DR or mild NPDR in the eye with the more severe disease (74.5%), 533 (58.7%) had at least 1 non-DM ocular finding necessitating referral.19

**Cost-effectiveness of Telemedicine DM Eye Care Programs**

The wide-spread acceptance and implementation of teleophthalmology programs for DM eye care is hindered by multiple factors, several of which center on the financial sustainability and cost-effectiveness of such programs. Present approaches that focus on screening large populations without regard for highly accurate determination of the severity of retinopathy, although reported to be cost-effective, may hinder the implementation of programs that provide higher standards of care. In addition, it remains to be determined if they can scale to address the vast need without losing long-term cost-effectiveness. A program fundamentally needs to reduce the public health burden of retinal examination by providing evidence-based care recommendations to patients at low risk for vision loss and identifying patients who require further ophthalmic intervention without placing an undue burden on present eye care systems. The cost-effectiveness of a nonmydriatic digital teleophthalmology system compared with a traditional clinic-based ophthalmoscopic examination with pupil dilation has been reported by multiple different authors.20,21 Using the JVN program as a model, decision analysis techniques, including Monte Carlo simulation, were used to compare the JVN with conventional clinic-based retinal examination among the entire populations with DM served by the Indian Health Service, the Department of Veterans Affairs, and the active duty Department of Defense. In the base-case economic analysis, the JVN was shown to be both less costly and more effective owing to its accurate assessment of DR severity. Although in this model the implementation of a category 3 program, such as the JVN, required a higher initial financial outlay and operational cost (an additional $1618 per additional patient treated with panretinal laser photocoagulation), it resulted in savings of $13 748 per severe vision loss event averted. Based on this model of economic analysis, a validated category 3 program that accurately assesses DR severity has the potential to be more effective than clinic-based retinal examination for identifying and accurately determining DR severity and preventing cases of severe vision loss in a cost-effective manner.21

**Approaches to speeding evaluation**

**Automated Retinal Image Analysis**

The automation of retinal image analysis is a critical step that will be required to increase the efficiency of image grading in an accurate and cost-effective manner. Presently, no single system for retinal image analysis can identify and gauge the extent of all sentinel lesions of DR. Most systems rely on identification of red or dark and yellow or bright lesions within the retina, and an extensive review on this topic has been published.22 There has been previously limited success in detecting less easily characterized lesions such as venous caliber abnormalities, intraretinal microvascular abnormalities, and retinal neovascularization. These lesions are the most difficult to detect both clinically and on ETDRS photographs but provide the best prognostic association with retinopathy progression and subsequent vision loss. Early results using matrix edge field algorithm has shown promise in detecting all 3 retinal lesions (Figure 2). Potentially, these morphologic mathematical algorithms can be fused to enhance performance and provide a global evaluation of retinopathy severity that can meet or even exceed current standards. The current JVN image database, which holds a growing number of over 600 000 retinal images, has been analyzed using a standardized protocol based on the ETDRS retinopathy severity and may serve as a testing resource for developing and testing image analysis algorithms.

**The Potential for “Point-of-Care” Retinal Image Analysis**

The prospect of retinal image analysis at the time of imaging may also be attained by adequate training of retinal imagers. A prospective comparative study involving 316 eyes of 158 patients who received retinal imaging at the Joslin Diabetes Center assessed the ability of certified JVN imagers to conduct category 1 and category 2 gradings using all JVN fields (Figure 1) at the time of retinal imaging.24 There were no cases of sight-threatening DR (severe NPDR or worse and/or DME) identified by JVN readers that were not identified by the imagers at the time of imaging. The JVN imagers identified 48 eyes (15.2%) with potentially sight-threatening DR (with at least moderate nonproliferative DR, proliferative DR, or diabetic macular edema present), of which 6 (1.9%) were graded as mild DR and no DME by JVN grad-
There were no cases of sight-threatening DR (severe or more advanced DR and/or DME) identified by JVN readers that were not identified by the imagers at the time of imaging. Of the 316 eyes, 279 (88%) were gradable by both JVN imager and graders, and had a value for agreement of 0.95 with a 100% sensitivity (95% CI, 0.89-1.00) and 97% specificity (95% CI, 0.95-0.99) in detecting vision threatening diabetic retinopathy. These findings may permit reliable deployment of category 1 and category 2 programs, with certified JVN imagers providing both the imaging and grading of JVN protocol retinal fields prior to formal category 3 JVN image grading, thus allowing more prompt triage of patients into appropriate acute ophthalmic care if indicated.

PREDICTIVE BIOMARKERS

Telemedicine programs have the potential to be deployed in a wide geographic area and access a diverse patient population, thus making such programs an excellent approach to collecting and evaluating specific epidemiologic questions. There have been substantial improvements in the telecommunication and technology infrastructure, now overcoming many of the previous difficulties with digital imaging and image archiving. With these advancements, it is essential that ocular telemedicine programs use validated image acquisition systems and standardized protocols to provide care that has been shown to be equivalent to retinal examinations in a clinical or research setting as appropriate.14,17 Furthermore, ocular DM telemedicine programs should allow integration of innovative research and the highest levels of clinical care. An ocular telemedicine program could help identify and evaluate predictive biomarkers of retinal disease by

Figure 2. Matrix edge field algorithms. A, Enhanced image of edge detection. B, Segmented image. C, Magnification of the areas of interest. D, Top left, image edge field strength showing a segment with sustained angle of orientation change (abnormality); top right, lesion location vessel region (green) and skeleton center line (red); bottom right, feature extraction (orientation angle of center line); bottom left, statistics crossing threshold only at lesion location (moving window averages of angle; 5 [blue], 6 [red], 7 [green], and 8 [black]).23 The x- and y-axes are pixel maps/coordinates.
leveraging its unique attributes of image-based retinal disease severity assessment, integrated medical record data acquisition, and access to diverse and underserved patient populations.

Presently, severe vision loss from DM remains a leading cause of visual impairment and is primarily due to the development of complications of PDR. Long-term population-based studies on the prevalence of PDR among patients with type 1 DM provide a glimpse of potential protective mechanisms that may be present in a subgroup of patients.25 The prevalence of PDR after 35 years of DM plateaus at approximately 65%. Unlike NPDR which will affect 97.5% of patients with type 1 diabetes after 15 years or more years of DM, nearly 40% of patients will never develop PDR even given extended durations of DM. Further confirmation of this observation is provided by studies conducted in patients with type 1 DM of 50 or more years’ duration.26,27 In a cohort of over 400 patients enrolled in the Joslin 50-year Medalist study with a mean duration of type 1 DM of 56 years (range, 50–79 years), a bimodal distribution of DR was observed: 50% of patients exhibited PDR, 41% had no to mild NPDR, and 9% had moderate or severe NPDR.26 The surprisingly large percentage of patients with extreme duration DM and yet no to mild DR suggests that there may be endogenous protective factors present in certain individuals that are effective despite many decades of high blood glucose exposure.28

CONCLUSIONS

The timely detection, evaluation, treatment, and careful follow-up of DR are crucial for preservation of vision in persons with DM. The burden placed on the health care system by the growing DM epidemic will necessitate a move away from the current acute care medical model toward novel approaches of remote site preventive care and automation of initial data analysis. Telemedicine and telehealth disciplines have the potential to address these challenges. It is essential that each telemedicine clinical care program with its associated imaging modality be rigorously validated to ensure that it meets the evidence-based standard of care. Similarly, findings in one system and/or program cannot necessarily be extrapolated to other unvalidated systems and/or programs. Methods to speed evaluation are being investigated and will rely on innovations in high-quality retinal images, automated retinal lesion detection, analysis through morphologic mathematical algorithms, and workflow enhancements. Future research initiatives are focusing on potential biomarkers to more readily identify at-risk individuals from within large populations and across wider geographic distributions. Although the current telemmedicine programs cannot yet meet the standards of an evidence-based comprehensive ophthalmological examination and the coordinated health care team approach, a major long-term goal includes improving the lives of people with DM through innovative care, education, and research supported in part by scalable telemedicine programs spanning all geographical, economic, and cultural boundaries.

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