Proceedings of the 2020 Winter Simulation Conference
K.-H. Bae, B. Feng, S. Kim, S. Lazarova-Molnar, Z. Zheng, T. Roeder, and R. Thiesing, eds.

EVALUATING DIABETIC RETINOPATHY SCREENING INTERVENTIONS IN A MICROSIMULATION MODEL

Breanna Swan
Siddhartha Nambiar
Priscille Koutouan
Maria E. Mayorga
Julie Ivy

Edwards P. Fitts, Department of Industrial and Systems Engineering
North Carolina State University
Raleigh, NC 27695, USA

Stephen Fransen

Retinal Care Inc.

608 Stanton L. Young Blvd
Oklahoma City, OK 73014, USA

ABSTRACT

Diabetic retinopathy (DR) is the leading cause of blindness for working age Americans. Early detection, timely treatment, and appropriate follow-up care reduce the risk of severe vision loss from DR by 95%, yet, less than 50% of people with diabetes adhere to the recommended screening guidelines. Diabetes is a complicated disease for patients and their physicians to manage. We developed a microsimulation integrating the natural history model of DR with a patient's interaction with the care system. We introduced a DR screening device in primary care, with and without care coordination by a medical professional, in two interventions to the current care path. We found the interventions increased adherence of patients with vision-threatening DR (VTDR) to follow-up eye care, decreased the number of 'unnecessary' visits in specialty eye care from patients without VTDR, and decreased the total years spent blind.

1 INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of blindness for working-age Americans and, in 2010, DR was responsible for moderate and severe vision impairment (20/60 - 20/400) in 3.7 million people worldwide (Leasher et al. 2016). In the United States, of the over 30 million people with diabetes, 28.5% will develop some stage of DR in their lifetime (Zhang et al. 2010). Early detection, timely treatment, and appropriate follow-up care reduce the risk of severe vision loss from DR by 95%. Yet, less than 50% of people with diabetes adhere to the recommended screening guidelines (Brechner et al. 1993; Kuo et al. 2005). Early detection is difficult without regular screening due to varying progression rates and a lack of symptoms, even in advanced stages. Regular and early screening and subsequent timely treatment are vital to preventing blindness. However, increasing numbers of patients with diabetes coupled with inequitable access to retinal specialists (Pandit et al. 2020), results in a large burden on the care system.

Diabetes is a complicated disease for patients and their physicians to manage. A comprehensive review by Piyasena et al. (2019) identified access to care, reluctance to change behavior, aversion to screening method, poor physician-patient communication, fear of laser treatment, and patient's DR knowledge as barriers preventing patients from DR screening and follow-up care. Barriers from the care perspective, including a lack of coordination between primary care and eye care, long waiting times due to a large number of patients per physician, and failure to refer patients to eye care from primary care, can also impede adherence to DR screening. Pandit et al. (2020) found that the number of retinal specialists was significantly

lower in poorer, sicker, and older communities. In this work, we tested two interventions to the current care process that aim to increase access to screening and reduce the number of low-risk patients utilizing primary eye care and retinal specialty resources unnecessarily.

One approach to solving this problem is to increase screening access with a simple hand-held DR screening device that is practical for a primary care office. One such device, RETeval (LKC Technologies, Inc., Gaithersburg, MD), can complete screening of both eyes in approximately five minutes without dilating the patient's eyes (Al-Otaibi et al. 2017; Maa et al. 2016). Due to its portability and ease of use, RETeval DR screening could take place at care points patients already visit such as primary care physician offices, pharmacies, or mobile clinics. The current care guidelines from the CDC (2018) and the American Academy of Ophthalmology (2019) recommend that all patients with diabetes annually visit a primary care provider and a primary eye care provider (an optometrist or an ophthalmologist) for DR screening. If identified as at increased-risk for vision-threatening diabetic retinopathy (VTDR), patients should also visit a retinal specialist for follow-up care. We introduce a DR screening device in primary care, with and without care coordination by a medical professional, in two interventions to the current care path.

We developed a microsimulation model of DR progression in patients with diabetes and patient's interaction with the care system. Markov models for type 1 and type 2 diabetes track the underlying disease progression in each patient built with data from large multi-center diabetes clinical trials (DCCT/EDIC Research Group 2017; Hayes et al. 2013; ACCORD Study Group 2007). We defined patient interaction with the care system and subsequent health outcomes from literature, expert opinion, and the PROTECT2 clinical trial (ClinicalTrials.gov, NCT03094819).

The purpose of this work is to make evidence-based comparisons between two proposed interventions and the current care guidelines. We use patient health outcomes, adherence behavior, and cumulative totals of visits to conclusions about the impact of moving DR screening to primary care and utilizing care coordination for patients at risk of the most severe outcomes of DR.

1.1 Relevant Literature

Markov and simulation models are extensively used to study the effects of chronic diseases and care interventions on patients and the care system. Markov chains model disease incidence and progression with examples including breast cancer (Tan et al. 2013), colorectal cancer (Frazier et al. 2000) and HIV/AIDS (Lee et al. 2014), and diabetes (Srikanth 2015). Discrete event simulations (DES) have been established as effective, safe ways to study care interventions such reducing appointment lead time in a rheumatology clinic (Swan et al. 2018) and improving efficiencies in emergency departments (Swan et al. 2019). In addition, population-level simulations can be used estimate the costs of interventions on chronic diseases such as colorectal cancer (Lich et al. 2019; Nambiar et al. 2018).

Utilizing both Markov and agent-based simulation models are especially useful for experimenting with care interventions for patients with non-communicable diseases (Currie and Monks 2019; Day et al. 2013). Work by Chalk et al. (2012) showed the necessity of modeling both underlying disease states and delivery of care for DR. Nambiar et al. (2018) and Lich et al. (2019) used a microsimulation model for population-level colorectal cancer screening and interventions. Specifically related to DR, simulation models have been used to compare screening strategies as a function of screening interval and modality and the type of health system (Brailsford et al. 2007; Davies et al. 2002). Interestingly, Davies et al. (2000) found referring patients for mild versus only severe DR stages did not affect the population-level years of sight saved.

The microsimulation model we developed in this work resembles models created in health economics literature (Standfield 2017) and uses a DES framework to model the individual interaction of patients with the care system; focusing on adherence and health outcomes rather than economic impact. We construct our disease progression model similar to Davies et al. (2000) and Brailsford et al. (2007) but allow for differing behavior of DR in patients with type 1 (T1DM) and type 2 (T2DM) diabetes. This microsimulation framework gives us the ability to analyze two screening interventions and their effects on both patients with diabetes and the care system.

2 MICROSIMULATION MODEL DESCRIPTION

The North Carolina Diabetic Retinopathy Simulation (NCDRS) model (Figure 1) was built at North Carolina State University in AnyLogic Personal Learning Edition 8.5.1 software. The model simulates a representative population of US adults with diabetes (Section 2.1). DR progresses each year for each patient over a 10-year period (Section 2.2). Patients annually interact with the care system according to the recommended DR care process (Section 2.3). The NCDRS model allows changes to the existing care process which we then evaluate via relevant patient-level and population-level metrics (Section 3).

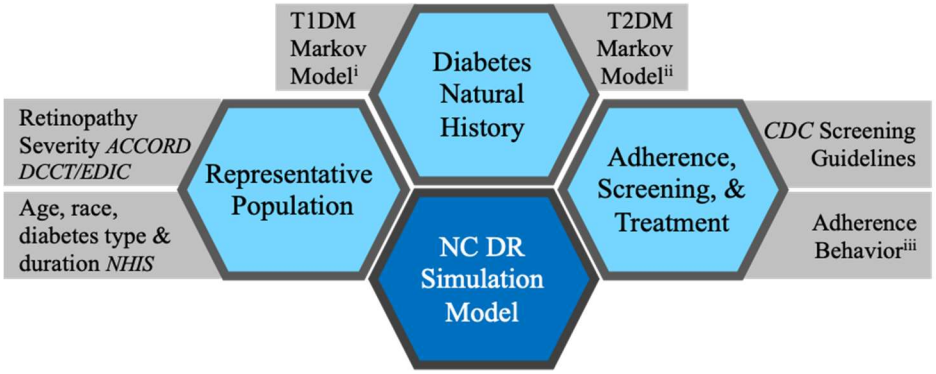

Figure 1: Overview of the three primary components (light blue) in the model (NCDRS) and associated data (grey) where *i*: (DCCT/EDIC Research Group 2017), *ii*: (Senthilvel et al. 2012; Srikanth 2015), *iii*: (Beckles et al. 1998; Keenum et al. 2016).

2.1 Population

NCDRS models a representative population of 10,000 US adults with diabetes using health and demographic information from the National Health Interview Survey and the National Health and Nutrition Examination Survey (Cowie and Eberhardt 1994). Diabetes type, age, gender, race, ethnicity, and duration of diabetes were assigned to each patient to reflect the demographics of US adults in 2009-2010 by type of diabetes. The presence of DR was assigned to the generated population based on diabetes type and duration using the global prevalence of DR (Yau et al. 2012). The initial stage of DR was assigned according to the patient population and DR progression in the DCCT/EDIC Clinical Trial (2017) and the ACCORD clinical trial (ACCORD Study Group 2007) given a patient's type and duration of diabetes (see Section 2.2).

2.2 Disease Progression

The progression of DR is characterized using a T1DM or T2DM Markov chain, assigned to each patient at the start of the simulation. Each Markov chain has six different DR states: no DR, mild non-proliferative DR (NPDR), moderate NPDR, severe NPDR, proliferative DR (PDR), and Blindness. The time to transition between states is distributed exponentially, with rates derived from literature sources depending on diabetes type. Figure 2 displays the relationship of each DR state and transition rates.

For both T1DM and T2DM, we derived the transition rate from one state to another for the Markov chain as the product of (1) the probability of transition between the two states given that a subject leaves the origin state and (2) the inverse of the average sojourn time within the origin state. We obtained both data elements for T1DM directly from the DCCT/EDIC Research Group (2017). We computed the two data elements for T2DM using the one-step (annual) probability transition matrix between DR states provided by Srikanth (2015). The authors did not include data for transitions out of the state no DR thus this value was obtained from Senthilvel (2012).

To reduce the number of patients ending in the blind state, we need to identify those patients at increased-risk of the vision-threatening stage of DR (VTDR) which includes severe NPDR and PDR.

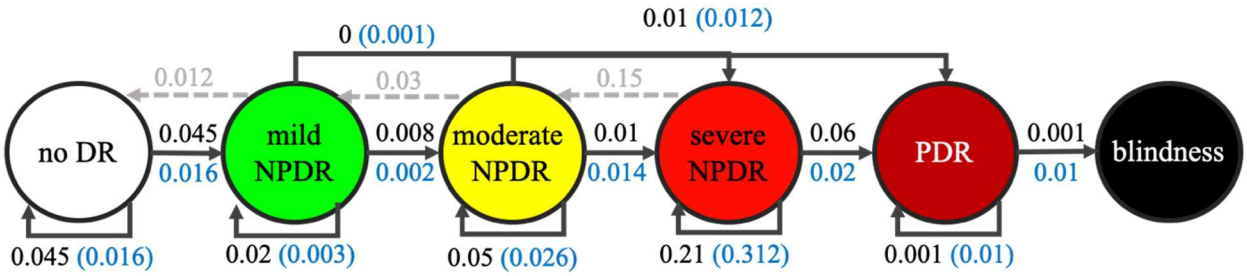

Figure 2: DR transitions rate diagram (month) for patients with type 1 (black) and type 2 (blue) diabetes.

2.3 Care Process

The recommended annual screening and treatment care process is shown in Figure 3 in which interactions occur between patients (blue) and providers (green). The two points at which our interventions impact patients are shown in yellow. If patients adhere to recommended screenings by attending the dark-blue events annually and adhering to recommended follow-up care and treatment (light-blue), they can avoid progression of DR (in red).

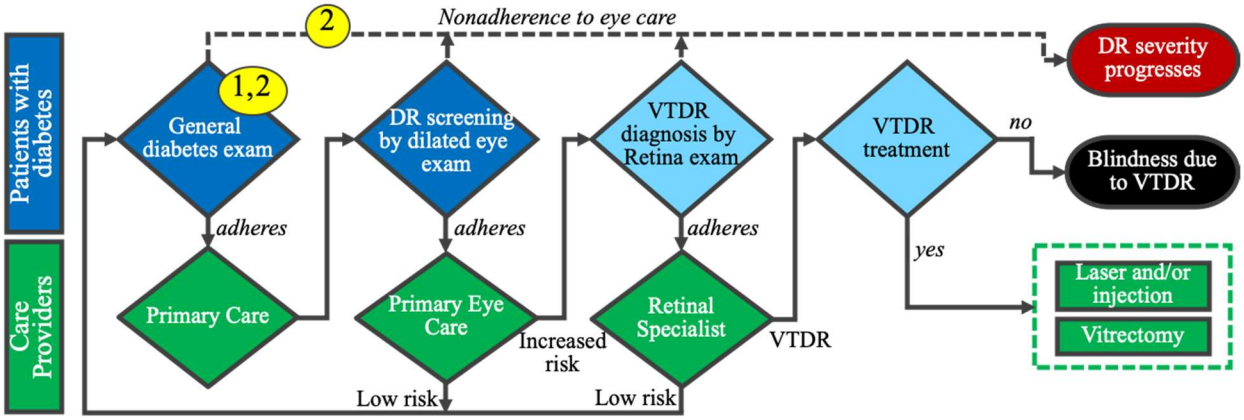

Figure 3: Typical DR care path with annual care recommendations (dark blue), follow-up care and treatment for patients identified at increased-risk for VTDR (light blue) and patient interactions with care providers (green). The dashed line indicates potential consequences of non-adherence to recommended DR care with our two Interventions in yellow (see Section 3).

In NCDRS, patients are modeled independently where each year they choose to visit primary care and primary eye care. The probabilities of adhering to the annual care guidelines are modeled as uniform distributions for primary care (0.701, 0.753) (Beckles et al. 1998) and primary eye care (0.33, 0.6) (Keenum et al. 2016; Lee et al. 2015; Murchison et al. 2017). While a primary care visit is not explicitly in care guidelines for DR, it is recommended for all patients with diabetes and, if they adhere to their primary care visit, patients are modeled as 50% more likely to visit an eye care provider (Storey and Haller 2016). In primary eye care, patients are screened for DR with a dilated eye exam and diagnosed as low-risk or increased-risk for VTDR. Patients at low risk of VTDR do not continue with eye care and resume the annual screening process. Patients at increased risk of VTDR are referred to a retinal specialist, with 90% adherence probability, for diagnosis confirmation and treatment.

Errors can occur throughout the care process. Patients with VTDR can remain undetected and untreated due to false-negative DR screening results and non-adherence to care guidelines. On the other hand, false-positive screening results can overload the system by sending patients without VTDR to retinal specialists,

filling appointments that should be available for patients with VTDR. The two interventions (in yellow, Figure 3) aim to reduce both false-positive and false-negative errors. Intervention 1 introduces primary care DR screening which we hypothesize will reduce the number of low-risk patients unnecessarily seeking specialty and primary eye care. Intervention 2 introduces both primary care DR screening and care coordination by a medical professional for patients with screening results indicating they have an increased-risk of VTDR. We hypothesize Intervention 2 will increase the number of patients who truly have VTDR adhering to follow-up care and treatment recommendations.

3 SIMULATED INTERVENTIONS

In the NCDRS model, patients interact annually with the care system as their DR progresses. We compared two interventions to the current DR care process (described in Section 2.3) while performing sensitivity analysis on the effectiveness of the interventions. Between replications, random number seeds for DR progression and for care engagement were held constant for each patient so we can isolate the effect of each intervention. In each of 50 replications, every patient was simulated for 10 years of their life. The number of replications chosen such that the half-width of annual number of patients in absorbing states (blind or treated) was less than 6. We chose to model 10 years to focus on the short-term results of our interventions. In addition, we did not trust the projection of disease progression and patient behavior beyond 10 years.

3.1 Intervention 1: DR Screening Device in Primary Care

Intervention 1 shifts DR screening to primary care where patients are diagnosed at low or increased risk for VTDR. Patients with an increased risk of VTDR are referred to primary eye care for a confirmation diagnosis while those with a low risk return for screening at primary care in one year.

For the patient, Intervention 1 reduces the number of required care visits for annual diabetes management from both primary care and primary eye care to just primary care. This intervention can also affect adherence behavior such that patients informed of increased risk of disease have a slight increase in adherence to follow-up care (Murchison et al. 2017). From the care-system perspective, Intervention 1 filters patients by risk of VTDR one step earlier in the care path, consequently reducing downstream appointments in specialty eye care.

NCDRS models primary care DR screening using RETeval, a handheld electroretinography and pupillography device with a five-minute test protocol. RETeval was selected due to data availability and established care paths through two clinical trials: Maa et al. (2016) and PROTECT2 (ClinicalTrials.gov, NCT03094819). Our model could be adapted to test any screening device; others in the market include IDx-DR (IDx Technologies Inc., Coralville, IA), IRIS (Intelligent Retinal Imaging Systems, Pensacola, FL), and smartphone applications (Savoy 2020; Naik et al. 2018). RETeval detects VTDR with 87% sensitivity and 78% specificity with a negative result indicating a patient is at low-risk for VTDR and a positive result indicating a patient is at increased-risk for VTDR.

3.2 Intervention 2: Care Coordination

Intervention 2 builds upon Intervention 1 to include both primary care DR screening and care coordination for patients diagnosed at increased risk of VTDR. In care coordination, a medical professional works with patients to help them understand their diagnosis, find a primary eye care provider, and make appointments.

The PROTECT2 clinical trial compared primary care RETeval screening and care coordination interventions to the current DR care system in a study of 500 participants. Information collected included screening results, primary care visits, care coordination (e.g., phone calls), and follow-up and treatment compliance. Care coordination was performed via phone calls which, after 90 days, resulted in an exam by an eye care provider for 80% of the increased risk population; most patients required more than five phone calls before adhering. In Intervention 2, primary care DR screening follows the same process as Intervention 1. Then, any patient identified as increased-risk for VTDR by the RETeval screening device receives care

coordination, represented by a number of calls. Each patient receives a randomly assigned number of calls based on data from PROTECT2 (Table 1, Row 1), then, conditional on the number of calls a patient receives, there is a probability the patient goes to the primary eye care provider (Table 1, Row 2).

Table 1: PROTECT2 data defining the distribution of calls per patient identified at increased-risk for VTDR by RETeval and, given a number of calls, the proportion of patients that adhere to follow-up care.

Number of Calls	**<3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**
Number of Patients	33	33	50	29	14	11	9	3	9
Adherence given Number of Calls	0.57	0.74	0.88	0.92	0.69	0.78	0.78	1	1

3.3 Sensitivity Analysis

Uncertainty in human behavior and screening accuracy can have an effect on adherence to DR current care guidelines. As such, we analyzed the sensitivity of our model to the accuracy of the primary care DR screening device by varying both sensitivity and specificity between 0.6 and 1, in increments of 0.01. In addition, while results are not included in this paper, we explored the sensitivity of our model to the underlying adherence assumptions and, as expected, the effect of Interventions 1 and 2 diminished when the underlying assumption of adherence to primary care and to primary eye care decreases.

3.4 Model Verification

Model outputs of proportions of patients adhering to each step of the care process and DR progression under current care guidelines were verified against data (Section 2). The number of calls a patient receives and subsequent probability of adherence in the model was verified against Table 1. For example, we verified the DR progression followed the trend in Day et al. (2013) in which patients overwhelmingly end in mild NPDR at the end of a 10-year simulation. Figure 4 confirms this by displaying the number of patients who start in healthstate *x* and end in healthstate *y* after the 10-year simulation; with the largest number of patients ending in mild NPDR.

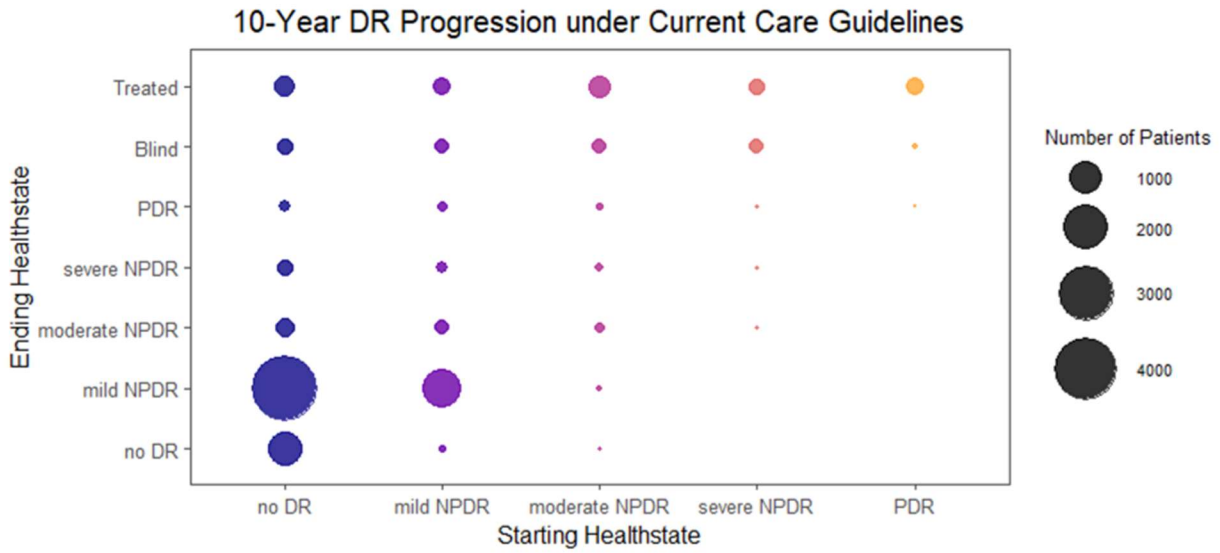

Figure 4: Number of patients progressing from a DR healthstate in Year 1 (x-axis) to a DR healthstate in Year 10 (y-axis), under the current care guidelines. The size of each circle corresponds to the number of patients in that path while the color signifies the starting healthstate.

4 RESULTS

The three DR care processes simulated are Intervention 0: the current care process, Intervention 1: primary care DR screening, and Intervention 2: primary care screening with care coordination. Each care process is compared using metrics from both the patient perspective, adherence, screening results, and health outcomes, and the provider perspective, the number of care visits. Each metric is filtered by the true underlying health state of the patient (no VTDR or VTDR) and by the step in the care process (primary care, primary eye care, and retinal specialty care). Statistically significant results are highlighted in each with result and assumptions of normality have been confirmed.

4.1 Screening and Adherence

We first analyze the effects of Interventions 1 and 2 on patient care visits and adherence, separated by true VTDR state. Table 2 shows the screening results and adherence averages over 10 years for primary care and primary eye care. The number and proportion of visits (Rows 1 and 2) represents those patients who adhere to their annual primary care and primary eye care visits. The number and proportion adhered (Rows 5 and 6) are the patients who received a positive DR screening result *and* moved on to the next step in the care process. We assume only those patients with positive screening results would be referred for follow-up care with a primary eye care provider (indicated by $(^{+})$). In the case of Intervention 0, this assumption changes such that *all* patients who go to primary care are referred to a primary eye care provider.

In separating by the true underlying VTDR state, we highlight the false positives and false negatives from screenings. Reduction of false positives lowers the number of 'unnecessary' eye care visits, or those patients without VTDR moving on to primary eye care. The bolded values in Table 2, Row 5, indicate that both Intervention 1 and 2 reduce false positives as compared to the current care system and, overall, reduce the number of patients without VTDR referred for follow-up care with a retinal specialist.

We also see that Interventions 1 and 2 increase the proportion of patients with VTDR adhering to follow-up eye care. Under the current care guidelines, we estimate only 55% of patients with VTDR see a primary eye care provider while over 74% of patients with VTDR went to a primary eye care provider in Intervention 2. This effect is further explored in the sensitivity analysis of Section 4.4.

Table 2: Adherence and screening results by true VTDR state with (-) and (+) representing a negative and positive screening result, respectively. The (+)(+) symbol in Row 7 represents those patients who received a positive screening result in both primary care and primary eye care. The $(^{+})$ indicates the denominator are both patients with a positive primary care screening result and patients who did not visit primary care.

		No VTDR						VTDR					
	Care Provider	Primary Care			Primary Eye Care			Primary Care			Primary Eye Care		
	Intervention	0	1	2	0	1	2	0	1	2	0	1	2
1	Number Visits	6,248	6,339	6,339	5,462	2,408	2,292	370	364	345	285	278	293
2	% Visits	0.73	0.73	0.73	0.64	0.65^{+}	0.62^{+}	0.71	0.71	0.71	**0.55**	**0.67^{+}**	**0.75^{+}**
3	(-) Screening Result	-	4,992	4,996	5,116	2,124	2,229	-	98	97	87.5	64	65
4	(+) Screening Result	-	1,347	1,343	347	169	178	-	248	266	197	214	228
5	Num Adhere Follow-up	4,373	1,198	1,312	**313**	**151**	**159**	227	223	239	162	175	187
6	% Adhere Follow-up	0.70	0.89	0.98	0.90	0.89	0.89	**0.62**	**0.84**	**0.96**	0.82	0.82	0.82
7	(+) (+) Results	-	-	-	-	92	99	-	-	-	-	143	156

4.2 Reducing the Burden of DR Screening

Building on Table 2, we highlight how Interventions 1 and 2 reduce the number of visits by patients without VTDR and increase the number of visits by patients with VTDR in primary eye care and retinal specialty care. The cumulative total visits in primary care, primary eye care, and retinal specialty care in

years 1, 5, and 10 are displayed in Figure 5, with stacked bars indicating visits by patients with VTDR (bottom) and patients without VTDR (top). As expected, the number of visits in primary care does not change between interventions, yet, we see a shift in the burden of DR screening from primary eye care to primary care in Interventions 1 and 2.

Interventions 1 and 2 result in fewer unnecessary visits by patients without VTDR in primary eye care and specialty retinal care in Interventions 1 and 2 compared to the current care process. The cumulative total of visits by patients without VTDR in primary eye care decreases between Intervention 0 and Intervention 1 (2) by 3,349 (3,223), 15,988 (15,399), and 27,251 (26,223)) total visits in years 1, 5, and 10, respectively. There is a slight increase between Interventions 1 and 2 due to care coordination increasing the adherence to recommended follow-up care among patients without VTDR receiving a false-positive DR screening result in primary care.

Figure 5 shows the increase in the proportion of patients with VTDR (compared to no VTDR) that make visits in primary eye care and retinal specialty care over a 1-, 5-, and 10-year period under both interventions. In addition, Interventions 1 and 2 increase the cumulative total visits by patients with VTDR in retinal specialty care. Comparing Intervention 0 and Intervention 1 (2), there is an increase of 28 (62), 91 (174), and 146 (277) cumulative visits by patients with VTDR for years 1, 5, and 10, respectively. Each difference is statistically significantly different (paired t-test, p-values < 1E-15).

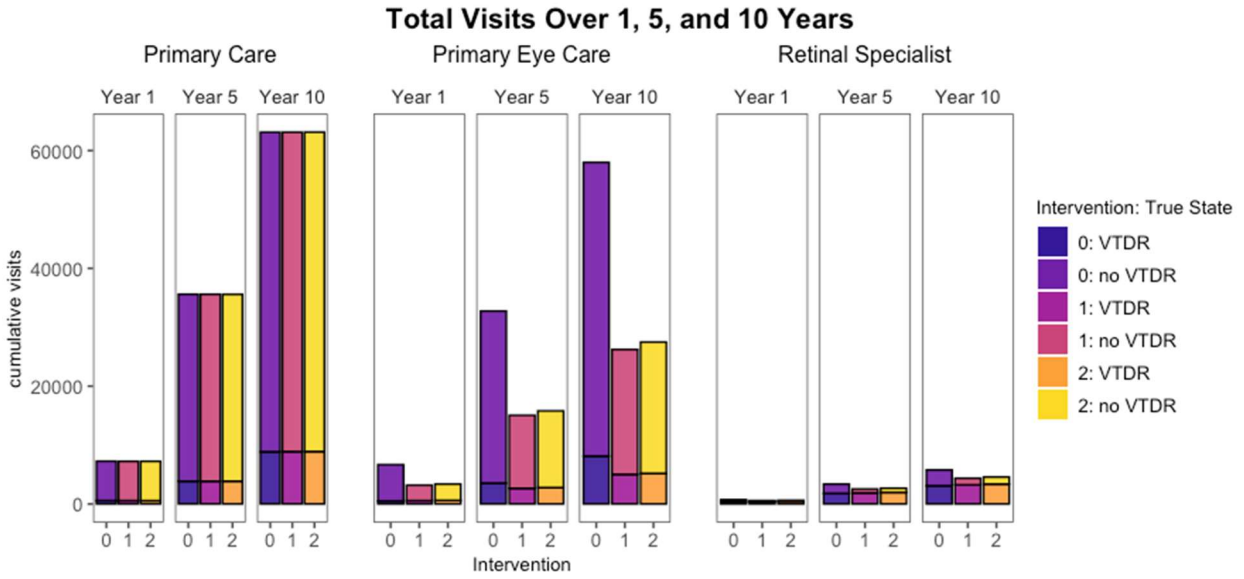

Figure 5: Total primary care, primary eye care, and retinal specialist visits for years one, five, and ten as the intervention changes (x-axis). Total visits are separated by the true VTDR state of patients (color). 95% confidence intervals are not visible due to their small size; ranging from 2 to 21 visits.

While Figure 5 shows us that both interventions enable a shift in the burden of DR screening towards primary care, Table 3 indicates that this shift is accompanied by improved patient health outcomes. Table 3 shows the total patient-years spent in each health state of no VTDR, VTDR, treated, or blind, with colors to match those categories displayed in Figure 5. The total *patient-years* is found by summing the number of patients in each health state over all 10 years and all 10,000 patients. For example, if one patient spent six years without VTDR and three years with VTDR while another patient spent seven years at with VTDR and was treated in year 8, the totals would be six "no VTDR" patient-years, ten VTDR patient-years, and two treated patient-years.

The number of patients who go blind decreases by about 3% under both interventions over the 10-year time horizon. Though not shown here, the population-level difference in cumulative years spent blind is

statistically significantly lower in Intervention 1 and 2, compared to Intervention 0, starting in Year 4 (paired t-test, p-values < 0.05). There is no statistically significant difference in the total patient-years spent blind between Interventions 1 and 2. In addition, the number of patients treated increases by 8% and 6% in 5 and 10 years, respectively, under Intervention 2 indicating that most patients are treated in a shorter time period due to enhanced screening guidelines under the Intervention 2.

Table 3: Cumulative Total Patient-Years in each health state. The (*) indicates the difference from Intervention 0 is statistically significant (p-value < 0.05).

	Intervention 0			**Intervention 1**			**Intervention 2**		
	Year 1	**Year 5**	**Year 10**	**Year 1**	**Year 5**	**Year 10**	**Year 1**	**Year 5**	**Year 10**
No VTDR	9,152	43,596	74,565	9,155	43,619	74,622	9,155	43,621	74,627
VTDR	560	2,482	4,381	542	2,381	4,169	523	2,260	3,946
Treated	209	2,798	7,789	226	2,914	8,039	245	3,033	8,256
Blind	78	1,124	3,265	77	1,086*	3,169*	77	1,087*	3,171*

4.3 Sensitivity Analysis: Most Severe Outcomes

We next analyze the effects of interventions on the most severe DR outcomes of blindness and treatment by exploring the sensitivity of our results to the accuracy of a primary care DR screening test. We vary two accuracy measures to capture this effect; specificity (the proportion of negative results out of all screened patients who truly do not have VTDR) and sensitivity (the proportion of positive results out of all screened patients who truly have VTDR). Table 4 displays the average number of patients ending in the blind or treated state over a selected range of sensitivity and specificity values in Interventions 1 and 2.

As the sensitivity of a primary care screening test increases, a higher proportion of patients with VTDR are referred for follow-up eye care and treatment. As expected, a screening test with high sensitivity lowers the number of patients who go blind and increases the number of patients treated, as seen in green in Table 4. Intervention 2 adds care coordination for patients with positive screening results thus amplifying the effects of increased screening sensitivity; resulting in fewer blind and more treated patients. While not displayed as a color in Table 4, the addition of care coordination in Intervention 2 leads to a statistically significant decrease (p-value < 0.05) in the number of patients who go blind and increase in the number of patients who are treated as compared to Intervention 1 over all values of sensitivity and specificity.

Table 4: Average number of patients ending in the health states blind or treated over a selected range of sensitivity and specificity values. Orange (*green*) cells are those that are statistically significantly less (*more*) than the current state (p-value < 0.05 for a paired t-test) while grey cells are those experiments which result in statistically the same number as the current state.

	Number Blind										Number Treated									
	Intervention 1					Intervention 2					Intervention 1					Intervention 2				
0.70	709	706	706	705	703	706	705	703	701	700	1,587	1,597	1,609	1,618	1,632	1,612	1,622	1,636	1,650	1,654
0.73	708	707	706	704	705	705	703	703	702	700	1,584	1,601	1,607	1,620	1,628	1,615	1,625	1,632	1,646	1,656
0.76	708	707	705	705	703	706	704	702	701	701	1,586	1,601	1,612	1,619	1,633	1,612	1,625	1,634	1,644	1,655
0.79	709	707	705	704	704	706	705	703	701	701	1,585	1,597	1,611	1,620	1,629	1,613	1,624	1,637	1,647	1,654
0.82	708	706	706	705	702	705	704	703	702	701	1,585	1,599	1,608	1,620	1,632	1,611	1,622	1,638	1,645	1,657
0.85	708	707	706	704	703	706	705	702	702	700	1,586	1,598	1,610	1,622	1,628	1,612	1,621	1,634	1,646	1,656
	0.70	**0.73**	**0.76**	**0.79**	**0.82**	**0.70**	**0.73**	**0.76**	**0.79**	**0.82**	**0.70**	**0.73**	**0.76**	**0.79**	**0.82**	**0.70**	**0.73**	**0.76**	**0.79**	**0.82**

specificity

sensitivity

The grey-green boundary in Table 4 show the cutoff at which the introduction of a primary care DR screening test statistically significantly treats more patients and prevents more patients from going blind

than the current state. In order to significantly improve identification of patients with VTDR, these results suggest a 'lower bound' exists on the sensitivity of a primary care DR screening device. Without care coordination, the sensitivity of a DR screening device should be at least 0.77 and with care coordination, the sensitivity should be around 0.74. We note, this analysis should be expanded upon provide a recommendation of higher accuracy.

5 DISCUSSION AND CONCLUSION

We successfully built a microsimulation model of DR progression in patients with diabetes and patients' interaction with the healthcare system. With this model, we can use metrics on patient health outcomes, adherence behavior, and cumulative totals of visits to make evidence-based conclusions about the impact of two interventions to the current DR care guidelines.

We found Interventions 1 and 2 are effective at reducing the number of 'unnecessary' retinal specialist visits by patients without VTDR, increasing the proportion of patients with VTDR being seen by primary eye and retinal specialists, and decreasing the number of blind patients while increasing the number of treated patients over a 10-year period. We also found a primary care DR screening test needs a sensitivity of at least 0.8 in order for there to be a significant increase in the number of patients treated. Portable DR screening devices, like the RETeval device which has a sensitivity of 87% for the detection of VTDR, reduce the complexity of diabetes management for patients and for providers. Both interventions enable a shift in the burden of care towards primary care; a shift that is accompanied by improved patient health outcomes.

Intervention 2 is being evaluated at several primary care clinical sites. Preliminary results demonstrate the RETeval screening device and care coordination reduces the number of eye care visits by 65% without decreasing VTDR sensitivity. This microsimulation model establishes a framework for testing interventions to alleviate barriers to screening and treatment of DR for patients in many environments. For example, sensitivity analysis on adherence assumptions would give insight into how robust interventions are when adherence and access to the primary care, primary eye care and a retinal specialty care changes from one region to the other. Furthermore, incorporating patient attributes such as age, race, gender, and ethnicity along with information related to patient behavior, barriers, and communication preferences may eliminate the need for separate clinical trials in population subgroups. Multiple interventions can be simulated on different segments of a population as the most effective intervention for two different population groups may be different. Finally, the effort associated with implementing interventions can be simulated by explicitly incorporating costs associated with provider visits, diagnosis and treatment of DR, intervention implementation, and other effort parameters within the simulation model.

Our work highlights how improvement to the DR care process such as shifting DR screening to primary care and adding care coordination has the potential to reduce the most severe outcomes of DR.

ACKNOWLEDGEMENTS

The authors would like to thank the NIH STTR grant program for partial funding of this work (1R41EY029917-01) and Dr. Kyle Hovey for his significant contributions.

REFERENCES

ACCORD Study Group. 2007. "Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods". *The American Journal of Cardiology* 99(12):21–33.

Al-Otaibi, H., M. D. Al-Otaibi, R. Khandekar, C. Souru, A. A. Al-Abdullah, H. Al-Dhibi, D. U. Stone and I. Kozak. 2017. "Validity, Usefulness and Cost of RETeval System for Diabetic Retinopathy Screening". *Translational Vision Science & Technology* 6(3):1-8.

Beckles, G. L. A., M. M. Engelgau, K. M. V. Narayan, W. H. Herman, R. E. Aubert, and D. F. Williamson. 1998. "Population-Based Assessment of the Level of Care Among Adults with Diabetes in the U.S.". *Diabetes Care* 21(9):1432–1438.

Brailsford, S. C., W. J. Gutjahr, M. S. Rauner, and W. Zeppelzauer. 2007. "Combined Discrete-Event Simulation and Ant Colony Optimisation Approach for Selecting Optimal Screening Policies for Diabetic Retinopathy". *Computational Management*

Science 4(1):59-83.

Brechner, R. J., C. C. Cowie, L. J. Howie, W. H. Herman, J. C. Will, and M. I. Harris. 1993. "Ophthalmic Examination Among Adults with Diagnosed Diabetes Mellitus". *Journal of the American Medical Association* 270(14):1714–1718.

CDC. 2018. "Watch Out for Diabetic Retinopathy", Centers for Disease Control and Protection. https://www.cdc.gov/features/diabetic-retinopathy/index.html, accessed 1st May 2020.

Chalk, D., M. Pitt, B. Vaidya, and K. Stein. 2012. "Can the Retinal Screening Interval Be Safely Increased to 2 Years for Type 2 Diabetic Patients Without Retinopathy?". *Diabetes Care* 35(8):1663–1668.

Cowie, C.C., M. I. Harris, and M. S. Eberhardt. 1994. "Frequency and Determinants of Screening for Diabetes in the US". *Diabetes Care* 17(10):1158–1163.

Currie, C. S., and T. Monks. 2018. "Modeling Diseases: Prevention, Cure and Management". In *Proceedings of the 2018 Winter Simulation Conference*, edited by M. Rabe, A. A. Juan, N. Mustafee, A. Skoogh, S. Jain, and B. J. Johansson, 440–454. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Davies, R., P. Roderick, C. Canning, and S. Brailsford. 2002. "The Evaluation of Screening Policies for Diabetic Retinopathy Using Simulation". *Diabetic Medicine* 19(9):762–770.

Davies, R., S. Brailsford, P. Roderick, C. Canning, and D. Crabbe. 2000. "Using Simulation Modelling for Evaluating Screening Services for Diabetic Retinopathy". *Journal of the Operational Research Society* 51(4):476–484.

Day, T. E., N. Ravi, H. Xian, and A. Brugh. 2013. "An Agent-Based Modeling Template for a Cohort of Veterans with Diabetic Retinopathy". *PloS One* 8(6):e66812.

DCCT/EDIC Research Group. 2017. "Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes". *New England Journal of Medicine* 376(16):1507–1516.

Frazier, A. L., G. A. Colditz, C. A. Fuchs, and K. M. Kuntz. 2000. "Cost-effectiveness of Screening for Colorectal Cancer in the General Population". *Journal of the American Medical Association* 284(15):1954–1961.

Hayes, A. J., J. Leal, A. M. Gray, R. R. Holman, and P. M. Clarke. 2013. "UKPDS Outcomes Model 2: A New Version of a Model to Simulate Lifetime Health Outcomes of Patients with Type 2 Diabetes Mellitus Using Data from the 30 Year United Kingdom Prospective Diabetes Study: UKPDS 82". *Diabetologia* 56(9):1925–1933.

Keenum, Z., G. McGwin, C. D. Witherspoon, J. A. Haller, M. E. Clark, and C. Owsley. 2016. "Patients' Adherence to Recommended Follow-Up Eye Care After Diabetic Retinopathy Screening in a Publicly Funded County Clinic and Factors Associated with Follow-Up Eye Care Use". *Journal of the American Medical Association Ophthalmology* 134(11):1221–1228.

Kuo, S., B. B. Fleming, N. S. Gittings, L. F. Han, L. S. Geiss, M. M. Engelgau, and S. H. Roman. 2005. "Trends in Care Practices and Outcomes Among Medicare Beneficiaries with Diabetes". *American Journal of Preventive Medicine* 29(5):396–403.

Leasher, J. L., R. R. A. Bourne, S. R. Flaxman, J. B. Jonas, J. Keeffe, K. Naidoo, K. Pesudovs, H. Price, R. A. White, T. Y. Wong, S. Resnikoff, and H. R. Taylor. 2016. "Global Estimates on the Number of People Blind or Visually Impaired by Diabetic Retinopathy: A Meta-Analysis from 1990 to 2010". *Diabetes Care* 39(9):1643–1649.

Lee, R., T. Y. Wong, and C. Sabanayagam. 2015. "Epidemiology of Diabetic Retinopathy, Diabetic Macular Edema and Related Vision Loss". *Eye and Vision* 2(1):1–25.

Lee, S., J. Ko, X. Tan, I. Patel, R. Balkrishnan, and J. Chang. 2014. "Markov Chain Modelling Analysis of HIV/AIDS Progression: A Race-Based Forecast in the United States". *Indian Journal of Pharmaceutical Sciences* 76(2):107-115.

Lich, K. H., M. C. O'Leary, S. Nambiar, R. M. Townsley, M. E. Mayorga, K. Hicklin, L. Frerichs, P. R. Shafer, M. M. Davis, and S. B. Wheeler. 2019. "Estimating the Impact of Insurance Expansion on Colorectal Cancer and Related Costs in North Carolina: A Population-Level Simulation Analysis". *Preventive Medicine* 129:105847.

Maa, A. Y., W. J. Feuer, C. Q. Davis, E. K. Pillow, T. D. Brown, R. M. Caywood, J. E. Chasan, and S. R. Fransen. 2016. "A Novel Device for Accurate and Efficient Testing for Vision-Threatening Diabetic Retinopathy". *Journal of Diabetes and Its Complications* 30(3):524–532.

Murchison, A. P., L. Hark, L. T. Pizzi, Y. Dai, E. L. Mayro, P. P. Storey, B. E. Leiby, and J. A. Haller. 2017. "Non-Adherence to Eye Care in People with Diabetes". *BMJ Open Diabetes Research and Care* 5(1):e000333.

Naik, S., C. C. Wykoff, W. C. Ou, J. Stevenson, S. Gupta, and A. R. Shah. 2018. "Identification of Factors to Increase Efficacy of Telemedicine Screening for Diabetic Retinopathy in Endocrinology Practices Using the Intelligent Retinal Imaging System (IRIS) Platform". *Diabetes Research and Clinical Practice* 140:265–270.

Nambiar, S., M. E. Mayorga, M. C. O'Leary, K. H. Lich, and S. B. Wheeler. 2018. "A Simulation Model to Assess the Impact of Insurance Expansion On Colorectal Cancer Screening at the Population Level". In *Proceedings of the 2018 Winter Simulation Conference*, edited by M. Rabe, A. A. Juan, N. Mustafee, A. Skoogh, S. Jain, and B. J. Johansson, 2701–2712. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Pandit, R. R., T. D. Wibbelsman, S. P. Considine, T. L. Jenkins, D. Xu, H. J. Levin, A. Obeid, and A. C. Ho. 2020. "Distribution and Practice Patterns of Retina Providers in the United States". *Ophthalmology* S0161-6420(20):30367-5. In Print, doi:10.1016/j.ophtha.2020.04.016.

Piyasena, M. M. P. N., G. V. S. Murthy, J. L. Y. Yip, C. Gilbert, M. Zuurmond, T. Peto, I. Gordon, S. Hewage, and S. Kamalakannan. 2019. "Systematic Review on Barriers and Enablers for Access to Diabetic Retinopathy Screening Services in Different Income Settings". *PloS One* 14(4):e0198979.

Savoy, M. 2020. "IDx-DR for Diabetic Retinopathy Screening". *American Family Physician* 101(5):307–308.

Senthilvel, V., R. Radhakrishnan, R. Sathiyamoorthi, S. Sumathi, and V. Jayanthi. 2012. "A Study on Multi Stages of Diabetic Retinopathy Among Diabetic Patients in Puducherry-Using Markov Chain Model Approach". *Advances in Applied Mathematical Biosciences* 3(1):49–55.

Srikanth, P. 2015. "Using Markov Chains to Predict the Natural Progression of Diabetic Retinopathy". *International Journal of Ophthalmology* 8(1):132-137.

Standfield, B. L. 2017. "Economic Modelling Methods for the Estimation of Resource Use, Cost-Effectiveness and Allocative Efficiency of Health Care Provision in a Capacity Constrained Health Care System". Ph.D. thesis, School of Medical Science, Griffith University, Queensland, Australia.

Storey, B. Y. P., and J. A. Haller. 2016. Retina Today: The Significance of Physician Communication in the Care of Patients. http://retinatoday.com/2016/09/the-significance-of-physician-communication-in-the-care-of-patients-with-diabetes/, accessed 1st May 2020.

Swan, B., C. Shevlin, A. Cho, and D. Phinney. 2018. "Simulation Tool to Evaluate Electronic Consultations in Rheumatology". In *Proceedings of the 2018 Winter Simulation Conference*, edited by M. Rabe, A. A. Juan, N. Mustafee, A. Skoogh, S. Jain, and B. J. Johansson, 2589–2599. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Swan, B., O. Ozaltin, S. Hilburn, E. Gignac, and G. McCammon. 2019. "Evaluating an Emergency Department Care Redesign: A Simulation Approach". In *Proceedings of the 2019 Winter Simulation Conference,* edited by N. Mustafee, K.-H. G. Bae, S. Lazarova-Molnar, M. Rabe, C. Szabo, P. Haas, and Y. J. Son, 1137–1147. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Tan, K. H. X., L. Simonella, H. L. Wee, A. Roellin, Y. W. Lim, W. Y. Lim, K. S. Chia, M. Hartman, and A. R. Cook. 2013. "Quantifying the Natural History of Breast Cancer". *British Journal of Cancer* 109(8):2035–2043.

Yau, J. W., S. L. Rogers, R. Kawasaki, E. L. Lamoureux, J. W. Kowalski, T. Bek, S. J. Chen, J. M. Dekker, A. Fletcher, J. Grauslund, and S. Haffner. 2012. "Global Prevalence and Major Risk Factors of Diabetic Retinopathy". *Diabetes Care* 35(3):556–564.

Zhang, X., J. B. Saaddine, C. F. Chou, M. F. Cotch, Y. J. Cheng, L. S. Geiss, E. W. Gregg, A. L. Albright, B. E. K. Klein, and R. Klein. 2010. "Prevalence of Diabetic Retinopathy in the United States, 2005-2008". *Journal of the American Medical Association* 304(6):649–656.

AUTHOR BIOGRAPHIES

BREANNA SWAN is a PhD candidate in Industrial and Systems Engineering at North Carolina State University. She holds a MS in Mathematics from University of Wisconsin - Milwaukee. Her research interests are in using data to support evidence-based decisions by integrating simulations, predictive analytics, and optimization models. Her email is bpswan@ncsu.edu.

SIDDHARTHA NAMBIAR holds a PhD in Industrial and Systems Engineering from North Carolina State University and an MS in Industrial Engineering from SUNY Buffalo. His research interests include stochastic modeling and simulation applied to health care. His email address is snambia@ncsu.edu.

PRISCILLE KOUTOUAN is a PhD student in Industrial and Systems Engineering at North Carolina State University. She holds a BS in Petroleum Engineering from the University of Houston. Her research interests include the use of simulation modeling, statistical and stochastic modeling to support health policy decision making. Her email address is prkoutout@ncsu.edu.

MARIA E. MAYORGA is a Professor of Personalized Medicine in Industrial and Systems Engineering at North Carolina State University. Her research interests include predictive models in health care, emergency response, and humanitarian logistics. She has authored over 65 publications and has been supported by NIH and NSF, among others. Her email is memayorg@ncsu.edu.

JULIE S. IVY is a Professor and Fitts Faculty Fellow in Industrial and Systems Engineering at North Carolina State University. Her research interests include mathematical modeling of stochastic dynamic systems as applied to healthcare and public health. Her research has been supported by the CDC, NSF, and NIH, among others. Her email is jsivy@ncsu.edu.

STEPHEN FRANSEN, MD, is a board-certified retina specialist with over 30 years' experience caring for patients with diabetic retinopathy. He serves as a faculty member at the University of Oklahoma, Dean McGee Eye Institute, and as the Chief Medical Officer with Retinal Care Inc. His email is stephen.fransen@retinalcare.com.