Novel strategy for screening of diabetic retinopathy

Diabetic retinopathy is the most common cause of blindness in adults. Visual deficiency is mainly caused from clinically significant macular edema or vision-threatening proliferative diabetic retinopathy. Recent advances in the treatment modalities, such as laser photocoagulation or with intraocular glucocorticoids or anti-vascular endothelial growth factor (VEGF) agents, can substantially reduce loss of vision. As timely application of such treatments is essential to make a difference in prognostic processes, the goal of retinopathy screening is the timely detection of retinopathy that would, without intervention, cause vision loss.

In patients with type 1 diabetes, annual screening for retinopathy starting 3–5 years after diagnosis has long been recommended, largely based on now-outdated epidemiological studies. However, the long-term benefits of intensive therapy on the clinical course of retinopathy are now well established, and recommendations for screening are being re-evaluated. Nathan et al.1, reporting for the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Research Group, provided data on an individualized schedule for screening for diabetic retinopathy in patients with type 1 diabetes mellitus. They analyzed almost 30 years of seven-field fundus photographs in a cohort of 1,441 patients with type 1 diabetes to simplify individualized risk assessments. They found that an accurate assessment of the risk of proliferative diabetic retinopathy or clinically significant macular edema was possible with the use of only the patient’s current retinopathy status and glycated hemoglobin levels.

A longitudinal Markov model2, which allowed for uneven visit intervals among patients, was used to estimate the cumulative incidence of transitions among five mutually exclusive retinopathy states that were based on Early Treatment Diabetic Retinopathy Study grades. State 1 corresponded to no retinopathy; state 2, mild non-proliferative diabetic retinopathy, including microaneurysms only; state 3, moderate non-proliferative diabetic retinopathy; and state 4, severe non-proliferative diabetic retinopathy. State 5 corresponded to any of the following: proliferative diabetic retinopathy; clinically significant macular edema or previous self-reported treatment with panretinal or focal photocoagulation; intraocular glucocorticoids; or anti-VEGF agents. Using this model, they calculated the probabilities of transitions from lower levels of retinopathy (states 1–4) to state 5 retinopathy with screening intervals of 1 month, 2 months, 3 months, 6 months, 9 months and 1–5 years. Progression from states 1 or 2 to state 5 retinopathy was unlikely over a period of ≥4 years, but progression was highly likely over shorter periods in patients with moderate (state 3) or severe (state 4) non-proliferative diabetic retinopathy. Their data suggest that a practical, evidence-based schedule for time to the next examination would be 4 years, 3 years, 6 months and 3 months for patients with states 1–4, respectively, for which the corresponding cumulative incidence of progression to state 5 retinopathy would be 2.9, 3.7, 6.6 and 14.4% (Table 1). Not surprisingly, within each retinopathy category, increasing glycated hemoglobin levels were associated with higher risks requiring more frequent screening schedules (Table 1). Non-glycemic factors had only small additive effects beyond the glycated hemoglobin level1.

The impact on cost-effectiveness was also discussed. The personalized schedules have the potential to reduce both the undetected time and the number of negative examinations at substantially lower cost. Over a 20-year period, annual screening resulted in an average of 18.4 examinations up to the time of detection of state 5 retinopathy vs just 7.7 examinations with the practical, evidence-based 4-year, 3-year, 6-month and 3-month schedule, for an average decrease of 10.7 (58% fewer) retinal examinations per patient. As digital photography costs approximately $200, and approximately 1 million patients have type 1 diabetes in the USA, it was estimated that the cost savings for eye screening would be approximately $1 billion over 20 years, as compared with routine annual screening
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The authors also provide a user-friendly Web application that can calculate a recommended time until the next eye examination on the basis of current retinopathy level and averaged glycated hemoglobin level. Scheduling retinopathy screenings at fixed intervals (e.g. annually) might be easier to implement than individualized scheduling based on retinal status. However, they believe that automated scheduling systems in common use by ophthalmologists could be used to cope with this potential barrier1.

A concern about screening intervals based on these variables is that determining the frequency of screening would be more complicated for patients and their doctors to follow. Even with current annual examination, more than one-third of patients do not follow the standard screening guidelines3. Another point to

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consider is that recent prevalent use of anti-VEGF and anti-inflammatory drugs might be changing the definition of diabetic retinopathy that requires treatment. Emerging data show that anti-VEGF and glucocorticoid therapies can reverse diabetic retinopathy, and even work better than panretinal and focal macular photocoagulation. Thus, screening algorithms and intervals might be better focused on more subclinical stages and entirely different in the future. Finally, validation studies involving patients with type 2 diabetes should be carried out before their findings in type 1 diabetes are generalized in all diabetes patients.

In conclusion, the study by Nathan et al. reflects an attempt to decrease the burden of screening on patients and on the healthcare system. On the basis of nearly 30 years of retinopathy assessments, they developed Markov transition models to estimate the probabilities of progression from preclinical levels of retinopathy to proliferative diabetic retinopathy or clinically significant macular edema that require treatment to preserve vision. A practical, evidence-based, individualized screening schedule would provide a shorter time during which proliferative retinopathy or macular edema would go undetected and would require substantially fewer examinations than the currently recommended annual screening.

**DISCLOSURE**

The author declares no conflict of interest.

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**Table 1** Screening schedule and the corresponding probability of progression from lower levels of retinopathy (state 1–4) to state 5 retinopathy (proliferative diabetic retinopathy or clinically significant macular edema)

| Overall | Glycated hemoglobin level (%) |
|---------|-------------------------------|
|         | 6    | 8    | 10   |

| State 1 to state 5 | Screening interval | Probability (%) |
|--------------------|--------------------|-----------------|
|                    | 4 years | 5 years | 5 years | 3 years |
| State 2 to state 5 | Screening interval | Probability (%) |
|                    | 3 years | 5 years | 4 years | 2 years |
| State 3 to state 5 | Screening interval | Probability (%) |
|                    | 6 months | 6 months | 3 months | 3 months |
| State 4 to state 5 | Screening interval | Probability (%) |
|                    | 3 months | 3 months | 1 month | 1 month |

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