# The Case for Biennial Retinopathy Screening in Children and Adolescents

ANN MAGUIRE, MB, BAD, BCH[1]
ALBERT CHAN, MAPP, STAT[1]
JANINE CUSUMANO[1]
STEPHEN HING, MBBS[1,2]
MARIA CRAIG, PHD[1,3]
MARTIN SILINK, MD[1,4]
NEVILLE HOWARD, MBBS[1]
KIM DONAGHUE, PHD[1,4]

**OBJECTIVE** — Current guidelines recommend annual retinopathy screening 2 years after onset (for pubertal-onset type 1 diabetes) and after 5 years (or age 11, whichever is earlier) for prepubertal onset. Our aim was to describe the natural history of retinopathy and to explore optimal retinal screening intervals for children and adolescents (aged <20 years) screened according to these guidelines.

**RESEARCH DESIGN AND METHODS** — More than 1,000 children and adolescents, followed longitudinally, were screened for retinopathy using seven-field stereoscopic fundus photography through dilated pupils. Of these, 668 had baseline and follow-up retinal screening. Using generalized estimating equations, we compared the risk of retinopathy with baselines at yearly intervals, in older and younger groups, in higher risk groups (diabetes duration >10 years or $HbA_{1c}$ >10% at any screening), and after stratification ≤10 and <10 years in duration.

**RESULTS** — After 1 year, retinopathy did not increase significantly in the older group ($n$ = 618, median $HbA_{1c}$ 8.7%, range 8.0–9.5), younger group ($n$ = 50, median $HbA_{1c}$ 8.5%, range 8.0–9.2), or the higher-risk groups. Retinopathy increased significantly after 2 years in the older group ($P$ = 0.003) but not until 6 years in the younger group ($P$ = 0.01). In the group with $HbA_{1c}$ >10% recorded at any visit, retinopathy increased significantly after 2 years ($P$ = 0.001) but not until 3 years in the group whose $HbA_{1c}$ was always ≤10% ($P$ = 0.003). After the second eye assessment, retinopathy did not increase significantly until 3 and 6 years later in the older and younger groups, respectively ($P$ = 0.028 and 0.014).

**CONCLUSIONS** — These results suggest that adolescents (in reasonable metabolic control) could safely be screened every 2 years rather than the currently recommended 1-year interval. In younger children, the next screening interval could be >2 years later. Individuals with especially poor control, duration >10 years, or significant retinopathy should be screened more frequently.

*Diabetes Care* **28:509–513, 2005**

To date there are no studies specifically addressing the frequency of screening for diabetic retinopathy in children and adolescents. Current annual screening recommendations for the pediatric population are based on national (1,2) and international consensus (3–5). In adults with both type 1 (6) and type 2 (7) diabetes without retinopathy, longer screening intervals are now being recommended subsequent to data from the Liverpool Diabetic Eye Study.

From the [1]Institute of Endocrinology and Diabetes and [2]Ophthalmology Department, The Children's Hospital at Westmead, Sydney, NSW, Australia; the [3]University of New South Wales, Sydney, New South Wales, Australia; and the [4]University of Sydney, Sydney, New South Wales, Australia.

Address correspondence and reprint requests to Ann Maguire, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Sydney, NSW 2145, Australia. E-mail: annm4@chw.edu.au.

Received for publication 9 June 2004 and accepted in revised form 9 November 2004.

**Abbreviations:** DCCT, Diabetes Control and Complications Trial; GEE, generalized estimating equation; MSFP, mydriatic stereoscopic fundal photography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



Loss of vision and blindness in persons with diabetes can be delayed or prevented by maintenance of good metabolic control and by early detection and treatment of vision-threatening retinopathy by regular eye examinations and timely intervention with laser treatment or through surgery in cases of advanced retinopathy (8–11).

To quantify screening intervals, it is important to understand the prevalence and natural history of retinopathy and to relate recommendations appropriately to the pediatric and adolescent population. Whereas there is a real and definite risk of blindness on a worldwide scale, it is rare to see more than background retinopathy in children and adolescents in developed countries.

In Australia, the prevalence of retinopathy, detected by stereoscopic fundal photography was reported to be 42% (no patient had more than mild background retinopathy) in a clinic population of adolescents with type 1 diabetes (12). In Europe and America, the reported prevalence in those screened by stereoscopic fundal photography varies from 10 to 35% (13–15). Of the many risk factors considered, longer duration of diabetes and poor glycemic control have been consistently reported as independent risk factors for retinopathy in children and adolescents (12,13,16–21). In a longitudinal cohort, we aim to describe the natural history of retinopathy and to explore optimal retinal screening intervals for children and adolescents screened according to current consensus guidelines (annual screening 2 years after onset for pubertal-onset type 1 diabetes and after 5 years or age 11, whichever is earlier, for prepubertal onset).

## RESEARCH DESIGN AND METHODS

— Included in this analysis were 668 children and adolescents with type 1 diabetes who had retinal screening at the Diabetes Complications Assessment Service at The Children's Hospital at Westmead. Patients were included if they had a baseline retinal screening performed between 1990 and

**Table 1—*Comparison of retinopathy progression in the older and younger age-groups***

| Age <11 years | | | | | Age ≥11 years | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Interval | *n* | Odds ratio | 95% CI | *P* | Interval | *n* | Odds ratio | 95% CI | *P* |
| 0–2 years | 35 | 1.03:1 | 0.28–3.77 | 0.975 | 0–1 years | 92 | 1.12:1 | 0.71–1.77 | 0.622 |
| 2–4 years | 41 | 0.85:1 | 0.21–3.37 | 0.811 | 1–2 years | 450 | 1.39:1 | 1.15–1.72 | 0.003* |
| 4–5 years | 24 | 2.37:1 | 0.67–8.31 | 0.177 | 2–4 years | 431 | 1.81:1 | 1.44–2.26 | <0.0005 |
| 5–6 years | 28 | 4.23:1 | 1.42–12.63 | 0.010 | 4–6 years | 167 | 2.24:1 | 1.62–3.10 | <0.0005 |
| ≥6 years | 16 | 2.72:1 | 0.59–12.4 | 0.196 | ≥6 years | 44 | 3.81:1 | 2.28–6.35 | <0.0005 |

2002 and at least one follow-up retinal assessment before 20 years of age.

Retinopathy was assessed using stereoscopic fundal photography of seven fields. The stereophotographs were taken with a Topcon Fundus Camera (TRC 50-VT; Tokyo Optical, Tokyo, Japan) after dilatation of the pupils with 1% cyclopentolate and 2.5% phenylephrine. Nonsimultaneous photographic pairs were taken of seven standardized fields in each eye and then viewed with a Donaldson Stereoviewer providing a three-dimensional representation of the fundus and enabling microaneurysms to be more easily distinguished from hemorrhages and artifacts.

Baseline and follow-up photographs from the entire set of 668 patients were graded by an ophthalmologist. A second grader also independently assessed 547 retinal photographs from 208 patients (31% of patients). Results were compared, and when retinopathy levels differed, both graders reviewed the photographs to reach consensus. When necessary, a grading supervisor was used to adjudicate. Agreement between the two graders was assessed by calculating a weighted κ score using quadratic weights. The κ value was 0.8, which indicates good agreement between graders.

The Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy was used (22,23). Retinopathy levels for each eye were classified as follows: level 10, no retinopathy; level 21, at least one microaneurysm or hemorrhage; level 31, microaneurysm plus one or more hemorrhage, exudate, venous bead, or loop; and level 41, moderately severe nonproliferative retinopathy. The level of retinopathy of the most severely affected eye was used for this analysis.

The ophthalmological assessment also included measurement of visual acuity, slit lamp examination of the anterior segment, and direct ophthalmoscopy. The following clinical and laboratory parameters were recorded at the time of each eye examination: height, weight, pubertal staging, blood pressure, and $HbA_{1c}$.

### Statistical methods

The statistical software SPIDA (Statistical Computing Laboratory, Sydney, Australia) was used for data analysis. Retinopathy progression (increase in the retinopathy level or a new occurrence of retinopathy) and regression (reduction in the retinopathy grading either to normal or a less severe grade) were assessed 1–2 years after the initial assessment (baseline). To include all assessments in longitudinal data analysis, generalized estimating equations (GEEs) were used to compare risk of retinopathy at yearly intervals to that at baseline, adjusting for effect of $HbA_{1c}$. Analyses were stratified by groups: *1*) the whole study group; *2*) older and younger subgroups; and *3*) higher-risk groups. The higher-risk groups were those with diabetes duration >10 years or $HbA_{1c}$ >10% at any screening visit. Statistical significance was taken as $P < 0.05$.

**RESULTS** — The patients were divided into two age-groups at baseline: <11 years at first retinopathy screening ($n = 50$, median $HbA_{1c}$ 8.5%, range 8.0–9.2%) and ≥11 years at first retinopathy screening ($n = 618$, median $HbA_{1c}$ 8.7%, range 8.0–9.5%). The prevalence of retinopathy at baseline screening was 16% (<11-year-old group) and 22% (≥11-year-old group). Overall, 136 of 668 patients had retinopathy at baseline screening (101 had level 21, 32 had level 31, and 3 had level 41). One to 2 years later, in the <11-year-old group, retinopathy regressed in 80% but progressed in none. In the ≥11-year-old group retinopathy regressed in 36% and progressed in 13%. None of the 668 patients had proliferative retinopathy, and none required laser therapy or surgery. All three patients with level 41 detected at baseline screening had regression of retinopathy by the next retinal screening. Using GEEs, at 1-year follow-up, there was no significant increase in retinopathy in the older or younger group. Retinopathy increased significantly after 2 years from the first eye assessment in the older group ($P = 0.003$) but not until 6 years in the younger group ($P = 0.01$) (Table 1). This effect was independent of $HbA_{1c}$. After the second eye assessment, retinopathy did not increase significantly until 3 years later in the older group ($P = 0.028$) and until 6 years later in the younger group ($P = 0.014$). This unexpected result may be explained by the decreasing sample size as we move further away from the baseline retinopathy screening event.

In the higher-risk groups (>10 years of diabetes duration or $HbA_{1c}$ >10% at any screening), at 1-year follow-up there was no significant increase in retinopathy. In the group with $HbA_{1c}$ >10% (documented at any screening), retinopathy increased significantly after 2 years ($P = 0.001$) but not until 3 years in the group whose $HbA_{1c}$ was always ≤10% ($P = 0.003$). Although patients with diabetes duration of >10 years were less likely to have an improvement in the level of retinopathy after 1 year (Table 2), there was still no significant increase in retinopathy at 1-year follow-up. The progression and regression patterns of retinopathy from first to last screening are demonstrated in Fig. 1. The median duration between the first and the last assessment was 3.1 years (interquartile range 2.0–4.4, range 0.5–8.6).

**CONCLUSIONS** — The current recommendations for retinopathy screening in children and adolescents are based on consensus viewpoint. The majority of professional bodies have adopted similar viewpoints and recommend annual reti-

**Table 2—*Effect of diabetes duration on retinopathy progression***

| | Retinopathy at baseline | | Progression of retinopathy 1–2 years later (%) | | | |
|---|---|---|---|---|---|---|
| Diabetes duration | % | Level | Regress to normal | Regress to lower grade | Persist | Progress |
| <10 years ($n$ = 429) | 14 (60 of 429) | 21: $n$ = 49; 31: $n$ = 9; 41: $n$ = 2 | 46 | 1 | 44 | 8 |
| >10 years ($n$ = 139) | 34 (47 of 139) | 21: $n$ = 27; 31: $n$ = 19; 41: $n$ = 1 | 23 | 17 | 43 | 17 |

nopathy screening beginning 2 years after onset (for pubertal-onset type 1 diabetes) and after 5 years (or age 11, whichever is earlier) for prepubertal onset (1–3). The Canadian guidelines recommend annual screening in those >15 years of age or after 5 years of diabetes (4). The American Academy of Pediatrics recommends annual screening beginning 3–5 years after diagnosis if >9 years of age (5). Although the American Diabetes Association recommends annual retinopathy screening for adults with type 1 diabetes (24), some professional bodies recommend biennial screening in adulthood (25,26). In the U.K., longer screening intervals are now being recommended for adults with both type 1 and type 2 diabetes who do not have retinopathy at baseline screening (6,7).

We were surprised to see that the prevalence of retinopathy had decreased in our clinic population. In 1994 we reported an overall prevalence of any retinopathy of 42% in those patients screened between 1989 and 1992 (12). The prevalence in the currently reported group is 16% in the younger group and 22% in the older group (<11 years old and ≥11 years old at baseline screening). This could be a direct consequence of the implementation of intensive insulin therapy following the Diabetes Control and Complications Trial (DCCT) results in 1993. Although the metabolic benefits of intensive therapy are not reflected in the median $HbA_{1c}$ of the currently reported group (8.6%) compared with 8.2% in the 1994 series, the currently reported group has a higher percentage of patients receiving multiple daily injections (33% compared with 13% in 1994, $P < 0.0001$), rather than twice-daily injections (67% compared with 87% in 1994, $P < 0.0001$). Therefore, the decreased prevalence of retinopathy may be due to fewer glucose excursions. We wondered if the decrease in prevalence of retinopathy was a result of the screening process itself; however, one would still expect there to be a metabolic correlate of such an improvement.

We wanted to update the current guidelines for retinopathy by specifically addressing the dilemmas facing the clinician deciding when to repeat the screening. To address these specific clinical dilemmas, we separately analyzed the <11-year-olds and ≥11-year-olds (as a surrogate cutoff for prepubertal and pubertal children, respectively). The current pediatric guidelines make different recommendations for prepubertal and pubertal children. Because there was no significant increase in the prevalence of any retinopathy after 1 year, it is unnecessary to repeat the screening annually. There was a significant increase in retinopathy after 2 years in the older group and after 6 years in the younger group. Although retinopathy did progress, the highest grade of retinopathy detected was level 41 (in 3 of 668 patients), and neither of these required treatment. From these results we believe that clinically significant, vision-threatening or treatment-requiring retinopathy will not be missed by extending the interval to 2 years.

Because diabetes duration and metabolic control have been consistently reported as risk factors for retinopathy and to further address real life clinical dilemmas, we analyzed specific higher-risk groups. Again, in this analysis, we found that after 1-year follow-up there was no significant increase in retinopathy. In the group with $HbA_{1c}$ >10% (documented at any screening), retinopathy increased significantly after 2 years but not until 3 years in the group whose $HbA_{1c}$ was always ≤10%. Although patients with dia-

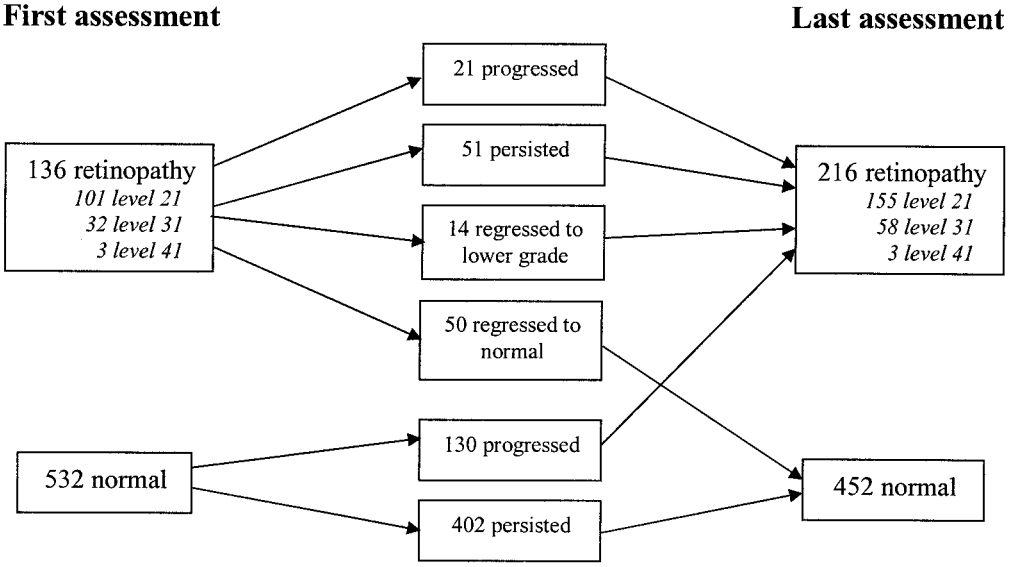


**Figure 1—*Change in retinopathy status from first to last retinal photograph.***

betes duration >10 years were less likely to have an improvement in the level of retinopathy after 1 year, there was still no significant increase in retinopathy at 1-year follow-up. Although these results suggest that it is safe to extend the screening interval in these higher-risk groups, our definition of what constitutes high risk is arbitrary. As the risk of complications increase directly with increased diabetes duration and $HbA_{1c}$, we feel that caution should be used for anyone who the clinician deems to be at higher risk and in whom follow-up is likely to be inconsistent.

Direct ophthalmoscopy, indirect ophthalmoscopy, nonmydriatic fundal photography, and mydriatic fluorescein angiography or mydriatic stereoscopic fundal photography (MSFP) are used to screen for retinopathy. The DCCT showed that MSFP is as sensitive as mydriatic fluorescein angiography in detection of retinopathy, and both of these methods are more sensitive than clinical examination by direct ophthalmoscopy alone (27). Our group found MSFP to be four times more sensitive than direct ophthalmoscopy alone in the detection of early background retinopathy (12). A recent systematic review looking at the effectiveness of retinopathy screening methods concluded that MSFP is the most sensitive method; however, direct ophthalmoscopy may be useful when photographs are ungradeable or for opportunistic case findings (28). Therefore, when resources permit, we recommend MSFP as the screening method of choice.

In keeping with data published previously from an audit of glycemic control in New South Wales and the Australian Capital Territory (29), ~75% of the currently reported group achieved an $HbA_{1c}$ <10%. Therefore, this recommendation may be applicable in a large proportion of our clinic population (depending on retinopathy screening results) and has significant resource utilization implications.

Current diabetes education programs coupled with the "fear of complications" may not be achieving optimum motivation for glycemic control. The retinopathy screening process itself may be a therapeutic, educational, and motivational event contributing to the reduction in retinopathy, which we have documented from 1994 to 2004. While redefining the appropriate screening frequency, we should not lose sight of these other potential benefits of screening.

The reason to increase the screening interval from 1 to 2 years are resource based and also are an attempt to resolve the inconsistency between existing pediatric and recent adult guidelines.

From our data we can say that in Australia and other developed countries with health care standards similar to those of Australia it is extremely unlikely that severe, vision-threatening or treatment-requiring retinopathy would be missed by extending the screening interval to 2 years for children and adolescents who access specialist diabetes services. In younger children the next screening interval could be >2 years later, provided there are no other risk factors. Individuals with other risk factors, poor glycemic control, or long diabetes duration should continue to be screened annually. When significant retinopathy is detected, screening should be annually or more frequently (depending on the severity of the retinopathy). In developing countries, especially when there is inadequate supply of insulin and in countries with different health care standards to Australia the onset of retinopathy may be earlier and the condition may progress more quickly. Therefore, these recommendations should be interpreted with caution outside of this setting.

**References**


1. Australasian Paediatric Endocrine Group: *APEG Handbook on Childhood and Adolescent Diabetes*. Sydney, Australasian Paediatric Endocrine Group, 1996
2. Queensland Health: Best practice guidelines for the management of type 1 diabetes in children and adolescents [article online], 2002. Available from www.health.qld.gov.au/publications/best_practice/16854.pdf. Accessed 7 September 2003
3. International Society for Pediatric and Adolescent Diabetes: *ISPAD Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents*. Zeist, the Netherlands, Medforum, 2000
4. Canadian Diabetes Association: Clinical Practice Guidelines for the Management of Diabetes in Canada. *CMAJ* 159:1–28, 1998
5. Koller HP, Fierson WM, Trese MT, Buckley EG, Ellis GS, Jr, Gross RD, Kivlin JD, Murphree AL, Schwartz RP, Lightner ES, LaFranchi S, Levine LS, Oberfield S, Owens RP, Reiter EO, Rosenfeld RG, Silverstein J, Arslanian S, Becker D, Drash A, Malone J, Klingensmith G, Levitsky L, Brink S: American Academy of Pediatrics: screening for retinopathy in the pediatric patient with type 1 diabetes mellitus. *Pediatrics* 101:313–314, 1998
6. Younis N, Broadbent DM, Harding SP, Vora JP: Incidence of sight-threatening retinopathy in type 1 diabetes in a systematic screening programme. *Diabet Med* 20:758–765, 2003
7. Younis N, Broadbent DM, Vora JP, Harding SP: Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *Lancet* 361:195–200, 2003
8. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
9. DCCT Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342:381–389, 2000
10. Early Treatment Diabetic Retinopathy Study Research Group: Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology* 98 (Suppl. 5):766–785, 1991
11. World Health Organization: Blindness [article online], 2003. Available from http://www.who.int/health_topics/blindness/en/. Accessed 7 September 2003
12. Fairchild JM, Hing SJ, Donaghue KC, Bonney MA, Fung AT, Stephens MM, Mitchell P, Howard NJ, Silink M: Prevalence and risk factors for retinopathy in adolescents with type 1 diabetes. *Med J Aust* 160:757–762, 1994
13. Falck AA, Kaar ML, Laatikainen LT: Prevalence and risk factors of retinopathy in children with diabetes: a population-based study on Finnish children. *Acta Ophthalmol* 71:801–809, 1993
14. Kernell A, Dedorsson I, Johansson B, Wickstrom CP, Ludvigsson J, Tuvemo T, Neiderud J, Sjostrom K, Malmgren K, Kanulf P, Mellvig L, Gjotterberg M, Sule J, Persson LA, Larsson LI, Aman J, Dahlquist G: Prevalence of diabetic retinopathy in children and adolescents with IDDM: a population-based multicentre study. *Diabetologia* 40:307–310, 1997
15. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: Retinopathy in young-onset diabetic patients. *Diabetes Care* 8:311–315, 1985
16. Kokkonen J, Laatikainen L, van Dickhoff K, Miettinen R, Tuominen M, Lautala P, Salmela P: Ocular complications in young adults with insulin-dependent diabetes

mellitus since childhood. *Acta Paediatr* 83:273–278, 1994
17. Klein R, Klein BE, Moss SE, Cruickshanks KJ: The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 105:1801–1815, 1998
18. Holl RW, Lang GE, Grabert M, Heinze E, Lang GK, Debatin KM: Diabetic retinopathy in pediatric patients with type-1 diabetes: effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control. *J Pediatr* 132:790–794, 1998
19. Kordonouri O, Danne T, Hopfenmuller W, Enders I, Hovener G, Weber B: Lipid profiles and blood pressure: are they risk factors for the development of early background retinopathy and incipient nephropathy in children with insulin-dependent diabetes mellitus? *Acta Paediatr* 85:43–48, 1996
20. Bonney M, Hing SJ, Fung AT, Stephens MM, Fairchild JM, Donaghue KC, Howard NJ, Silink M: Development and progression of diabetic retinopathy: adolescents at risk. *Diabet Med* 12:967–973, 1995
21. Danne T, Weber B, Hartmann R, Enders I, Burger W, Hovener G: Long-term glycemic control has a nonlinear association to the frequency of background retinopathy in adolescents with diabetes: follow-up of the Berlin Retinopathy Study. *Diabetes Care* 17:1390–1396, 1994
22. Klein R, Klein BEK, Moss SE: The Wisconsin epidemiological study of diabetic retinopathy. IX. Four year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 107:237–143, 1989
23. Diabetic Retinopathy Study Research Group: Diabetic Retinopathy Study Research Group. Report 7. A modification of the Airlie House classification of diabetic retinopathy. *Invest Opthalmol Vis Sci* 21: 210–226, 1981
24. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 (Suppl. 1):33S, 2003
25. Retinopathy Sub-Committee of Australian Diabetes Association: ADS Position Statement: Diabetes and the eye [article online], 1996. Available from www.racp.edu.au/ads/Diabetes_and_the_Eye.pdf. Accessed 7 September 2003
26. Writing Group for Therapeutic Guidelines: *Therapeutic Guidelines: Endocrinology*. Melbourne, Australia, Therapeutic Guidelines, 1997
27. DCCT Research Group: Color photography vs fluorescein angiography in the detection of diabetic retinopathy in the diabetes control and complications trial: the Diabetes Control and Complications Trial Research Group. *Arch Ophthalmol* 105:1344–1351, 1987
28. Hutchinson A, McIntosh A, Peters J, O'Keeffe C, Khunti K, Baker R, Booth A: Effectiveness of screening and monitoring tests for diabetic retinopathy: a systematic review. *Diabet Med* 17:495–506, 2000
29. Handelsman P, Craig ME, Donaghue KC, Chan A, Blades B, Laina R, Bradford D, Middlehurst A, Ambler G, Verge CF, Crock P, Moore P, Silink M: NSW/ACT $HbA_{1c}$ Study Group: homogeneity of metabolic control in New South Wales and the Australian Capital Territory, Australia. *Diabetes Care* 24:1690–1691, 2001