# Disease Course of Patients with Unilateral Pigmentary Retinopathy

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**Purpose.** To evaluate the change in ocular function by eye in patients with unilateral pigmentary retinopathy.

**Methods.** Longitudinal regression was used to estimate mean exponential rates of change in Goldmann visual field area (V4e white test light) and in full-field electroretinogram (ERG) amplitudes to 0.5- and 30-Hz white flashes in 15 patients with unilateral pigmentary retinopathy. Snellen visual acuity was assessed case by case.

**Results.** Mean annual rates of change for the affected eyes were −4.9% for visual field area, −4.7% for ERG amplitude to 0.5-Hz flashes, and −4.6% for ERG amplitude to 30-Hz flashes. All three rates were faster than the corresponding age-related rates of change for the fellow normal eyes ($P = 0.0006$, $P = 0.003$, $P = 0.03$, respectively). An initial cone ERG implicit time to 30-Hz flashes in affected eyes ≥40 ms predicted a faster mean rate of decline of visual field area and of ERG amplitude to 0.5- and 30-Hz flashes ($P < 0.0001$ for all three measures). The visual acuity of affected eyes was more likely to decrease in patients presenting at >35 years of age than in patients presenting at a younger age ($P = 0.0004$).

**Conclusions.** The affected eye in unilateral pigmentary retinopathy shows a progressive loss of peripheral retinal function that cannot be attributed to aging alone and that is faster in eyes with a more prolonged initial cone ERG implicit time. Patients presenting at >35 years of age are at greater risk for losing visual acuity. (*Invest Ophthalmol Vis Sci.* 2011;52:9244–9249) DOI:10.1167/iovs.11-7892

Unilateral pigmentary retinopathy is a rare, sporadic disease in which patients have one eye affected with pigmentary retinopathy and a normal fellow eye.[1–7] This contrasts with the typical forms of retinitis pigmentosa in which both eyes are affected and for which pathogenic gene mutations have generally been identified.[8–12] Nonetheless, the fundus appearance and reduced electroretinogram (ERG) amplitudes of affected eyes with unilateral pigmentary retinopathy are comparable to those of typical forms of bilateral retinitis pigmentosa.[1–7]

The criteria of Francois and Verriest for an authentic case of unilateral pigmentary retinopathy (i.e., idiopathic form) are that the affected eye must show the clinical signs of pigmentary retinopathy; the healthy eye must not show any signs of pigmentary retinopathy and must have a normal full-field ERG; and infectious, inflammatory, and vascular etiologies of pigmentary retinopathy have been excluded.[3] Several case studies of unilateral pigmentary retinopathy have been reported but all previous studies were concerned with confirming the diagnosis and the stability of the fellow normal eye rather than the analysis of rates of change in ocular function of the affected eye.[1–7] No previous report of unilateral pigmentary retinopathy has described rates of change in ocular function over follow-up to determine the course of the disease. For example, a recent study followed four patients for 6 to 11 years and reported progressive loss of visual acuity, visual field, and ERG amplitude in the affected eye of three of the four cases without providing follow-up values for these affected eyes.[6]

The present study was done to estimate, for the first time, the mean annual rates of change in retinal function in the affected eyes of a cohort of patients with unilateral pigmentary retinopathy. Results were compared with the age-related rates of change for their normal fellow eyes.

## Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School. From a database of approximately 8000 patients with retinitis pigmentosa, we identified 15 patients with unilateral pigmentary retinopathy (5 males and 10 females, 20 to 61 years of age at their initial visit) with two or more visits spaced by at least 3 years (follow-up ranged from 3 to 33 years, with a mean of 9 years).

Patients included in this study were identified elsewhere based on a routine ocular examination and were referred to the Massachusetts Eye and Ear Infirmary for a retinal evaluation because of pigment seen in one eye. Our diagnosis of unilateral pigmentary retinopathy was based on the findings of one eye with retinal arteriolar attenuation, bone-spicule pigmentation around the fundus periphery, a constricted visual field, and subnormal full-field ERG amplitudes, and a fellow eye with a normal fundus appearance and normal ocular function. These 15 patients had no known family history of retinitis pigmentosa and no history of trauma or retinal inflammatory disease.

Best-corrected Snellen visual acuities, Goldmann kinetic visual field areas (V4e white test light), and full-field ERG amplitudes to 0.5- and 30-Hz white full-field flashes were measured at each visit, with test conditions described previously.[8,9,11–13] Table 1 lists the age and ocular function measurements from the affected eye for each patient at the initial and final visits (mean values are provided at the bottom). The visual acuity at the initial visit ranged from 20/20 to 20/400 (mean = 20/25). The visual field area at the initial visit ranged from 298 to 14,578 deg$^2$ (mean = 5909 deg$^2$; lower norm = 11,399 deg$^2$). The ERG amplitude to 0.5-Hz white flashes at the initial visit ranged from 2.10 to 205 $\mu$V (mean = 65.8 $\mu$V; lower norm = 350 $\mu$V). The ERG amplitude to 30-Hz white flashes at the initial visit ranged from 0.33 to 39.0 $\mu$V (mean = 10.4 $\mu$V; lower norm = 50 $\mu$V).

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**Table 1.** Ocular Function of the Affected Eyes of Patients with Unilateral Pigmentary Retinopathy

| | | Initial Visit | | | | | Final Visit | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient ID | Sex | Age (y) | VA | Visual Field Area ($deg^2$)* | 0.5-Hz ERG ($\mu$V)* | 30-Hz ERG ($\mu$V)* | Age (y) | VA | Visual Field Area ($deg^2$)* | 0.5-Hz ERG ($\mu$V)* | 30-Hz ERG ($\mu$V)* |
| 25840 | F | 20 | 20/20 | 8,361 (103) | 2.11 | 0.92 | 23 | 20/20 | 7,778 (99) | NA | 0.76 |
| 13391 | F | 20 | 20/20 | 9,388 (109) | 61.70 | 10.10 | 28 | 20/20 | 5,208 (81) | 29.40 | 3.64 |
| 687 | F | 20 | 20/30 | 11,176 (119) | 167.00 | 29.00 | 60 | 20/25 | 6,918 (94) | 66.00 | 10.30 |
| 5470 | F | 20 | 20/20 | 469 (24) | 11.00 | 0.50 | 36 | 20/20 | 174 (15) | 3.50 | 0.23 |
| 11172 | M | 20 | 20/20 | 298 (19) | 3.10 | 0.33 | 40 | 20/20 | 206 (16) | NA | 0.27 |
| 15711 | F | 20 | 20/25 | 3,682 (68) | 14.70 | 1.26 | 42 | 20/30 | 3,178 (64) | 2.30 | 0.10 |
| 25094 | M | 20 | 20/20 | 14,578 (136) | 160.00 | 19.00 | 41 | 20/20 | 15,835 (142) | 127.00 | 22.00 |
| 11345 | M | 20 | 20/20 | 10,300 (114) | 23.50 | 11.70 | 55 | 20/20 | 331 (20) | 1.58 | 0.47 |
| 6570 | M | 38 | 20/20 | 2,490 (56) | 32.00 | 2.50 | 42 | 20/70 | 2,504 (56) | 29.00 | 3.30 |
| 26346 | F | 40 | 20/400 | 6,148 (88) | 96.00 | 39.00 | 43 | 20/400 | 7,392 (97) | 100.00 | 34.00 |
| 14943 | F | 45 | 20/20 | 14,100 (134) | 205.00 | 27.00 | 51 | 20/30 | 10,467 (115) | 146.00 | 15.00 |
| 14828 | F | 53 | 20/30 | 1,958 (50) | 44.00 | 7.40 | 68 | 20/60 | 1,655 (46) | 25.00 | 5.02 |
| 11250 | F | 54 | 20/30 | 2,391 (55) | 53.00 | 4.30 | 59 | 20/100 | 1,233 (40) | 36.00 | 4.10 |
| 19820 | F | 60 | 20/25 | 2,211 (53) | 106.00 | 1.60 | 70 | 20/50† | 1,862 (49) | 49.00 | 0.87 |
| 13209 | M | 61 | 20/30 | 1,086 (37) | 7.40 | 1.10 | 64 | 20/40 | 584 (27) | 9.10 | 1.12 |
| Mean | | 39 | 20/25 | 5,909 | 65.80 | 10.40 | 48 | 20/30 | 4,355 | 41.60 | 6.75 |

The visual field equivalent circular diameter is designated in parentheses. VA, best-corrected Snellen visual acuity; ERG, ERG amplitude; NA, not available.

* Lower norms are 11,399 $deg^2$ for visual field area (V4e white test light), 350 $\mu$V for electroretinogram amplitude to 0.5-Hz white flashes, and 50 $\mu$V for electroretinogram amplitude to 30-Hz white flashes.

† Pseudophakic.

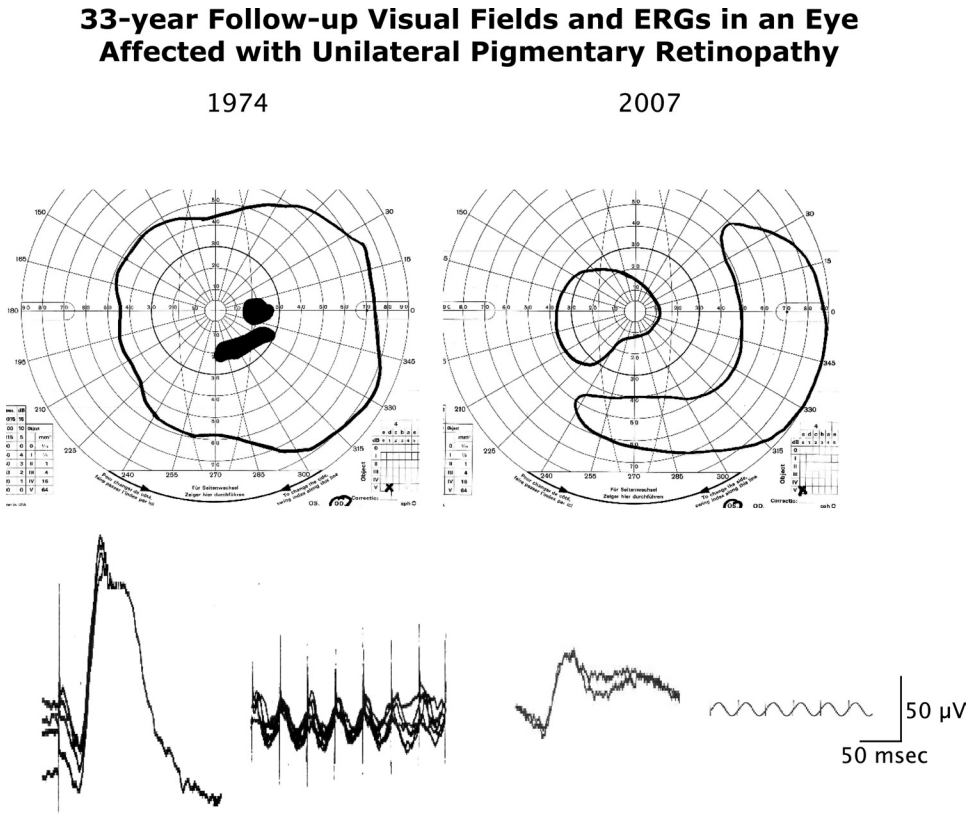


**FIGURE 1.** Goldmann visual fields to the V4e white test light and full-field ERGs spanning 33 years from patient 687 with unilateral pigmentary retinopathy, to illustrate disease progression in the affected eye. The cone responses to 30-Hz white flashes in 2007 were obtained with narrow bandpass filtering and computer averaging.

For estimating mean rates of change, censoring criteria were applied to the data as in previous longitudinal studies of retinitis pigmentosa.[8,9,11,12] We censored visual acuities of 20/20, except those that followed a lower value, to minimize a ceiling effect[8] and initial visual acuities < 20/100 to minimize a floor effect.[9] One patient (19820) became pseudophakic at follow-up and, therefore, we censored the follow-up visual acuity.[12] Censoring was not required for visual field areas, which were all >78 deg$^2$ (i.e., equivalent to a diameter of >10°).[8] For ERG amplitudes to 0.5-Hz white flashes, we censored follow-up values after the amplitude had fallen to <2.5 $\mu$V to minimize a floor effect.[9] For ERG amplitudes to 30-Hz white flashes, we censored initial values <0.68 $\mu$V and follow-up values after the amplitude had fallen to <0.34 $\mu$V to minimize a floor effect.[9]

We then converted visual field areas and ERG amplitudes to natural logarithms because an exponential model provides a good fit for describing disease progression in patients with typical retinitis pigmentosa.[8–17] Repeated-measures longitudinal regression (performed with PROC MIXED of SAS, version 9.1.3; SAS Institute Inc., Cary, NC) was used to estimate the mean rates of change for the visual field and the ERG outcome measures based on the affected eyes, on the normal eyes, and on the difference between the fellow eyes at each visit; this procedure, which can handle unbalanced data, assigns greater weight to patients with more examinations and longer follow-up. However, only seven patients retained usable longitudinal data for visual acuity analysis after censoring; we considered this sample too small to estimate reliably a mean rate of visual acuity change and, instead, assessed change in visual acuity on a case-by-case basis.

## RESULTS

A patient with unilateral pigmentary retinopathy, seen initially at 27 years of age and followed for 33 years (our patient with the longest follow-up), showed progressive loss of visual field from a small midperipheral scotoma to a complete midperipheral scotoma in the affected eye. The patient also showed a reduction of the mixed rod + cone ERG to 0.5-Hz white flashes and of the cone ERG to 30-Hz white flashes in that eye over the same period (Fig. 1).

**TABLE 2.** Mean Annual Rates of Change in Remaining Visual Field Area and ERG Amplitude in Unilateral Pigmentary Retinopathy

| Ocular Function | *n* | Affected Eye Mean ± SEM (Geometric Mean)* | *P** | *n* | Normal Eye Mean ± SEM (Geometric Mean)* | *P** | *P*† |
|---|---|---|---|---|---|---|---|
| Visual field area ($\log_e$ deg$^2$) | 15 | −0.050 ± 0.013 (−4.9%) | 0.001 | 15 | 0.002 ± 0.003 (0.2%) | 0.45 | 0.0006 |
| ERG amplitude to 0.5-Hz white flashes ($\log_e$ $\mu$V) | 14 | −0.048 ± 0.011 (−4.7%) | 0.0001 | 15 | −0.014 ± 0.003 (−1.4%) | <0.0001 | 0.003 |
| ERG amplitude to 30-Hz white flashes ($\log_e$ $\mu$V) | 13 | −0.047 ± 0.014 (−4.6%) | 0.002 | 15 | −0.012 ± 0.004 (−1.2%) | 0.006 | 0.03 |

* Test of mean $\log_e$ change versus zero (using PROC MIXED of SAS).

† Test of mean $\log_e$ change for the difference between the affected and normal eyes (using PROC MIXED of SAS).

The *n* for *P*† is equal to the *n* for the affected eye. The table reflects censoring of one affected eye for the $\log_e$ ERG amplitude to 0.5-Hz white flashes and censoring of two affected eyes for the $\log_e$ ERG amplitude to 30-Hz white flashes.

**TABLE 3.** Effects of Initial Cone ERG Implicit Time on the Mean Annual Rate of Decline of Ocular Function in the Affected Eyes of Patients with Unilateral Pigmentary Retinopathy

| Ocular Function | Implicit Time <40 ms | | Implicit Time ≥40 ms | | *P** |
|---|---|---|---|---|---|
| | *n* | Mean ± SEM (Geometric Mean)* | *n* | Mean ± SEM (Geometric Mean)* | |
| Visual field area ($\log_e$ deg$^2$) | 7 | −0.018 ± 0.009 (−1.8%) | 8 | −0.151 ± 0.016 (−14%) | <0.0001 |
| ERG amplitude to 0.5-Hz white flashes ($\log_e$ $\mu$V) | 7 | −0.029 ± 0.007 (−2.9%) | 7 | −0.133 ± 0.015 (−12%) | <0.0001 |
| ERG amplitude to 30-Hz white flashes ($\log_e$ $\mu$V) | 6 | −0.025 ± 0.013 (−2.5%) | 7 | −0.119 ± 0.023 (−11%) | <0.0001 |

* Test of difference in mean rate (using PROC MIXED of SAS).

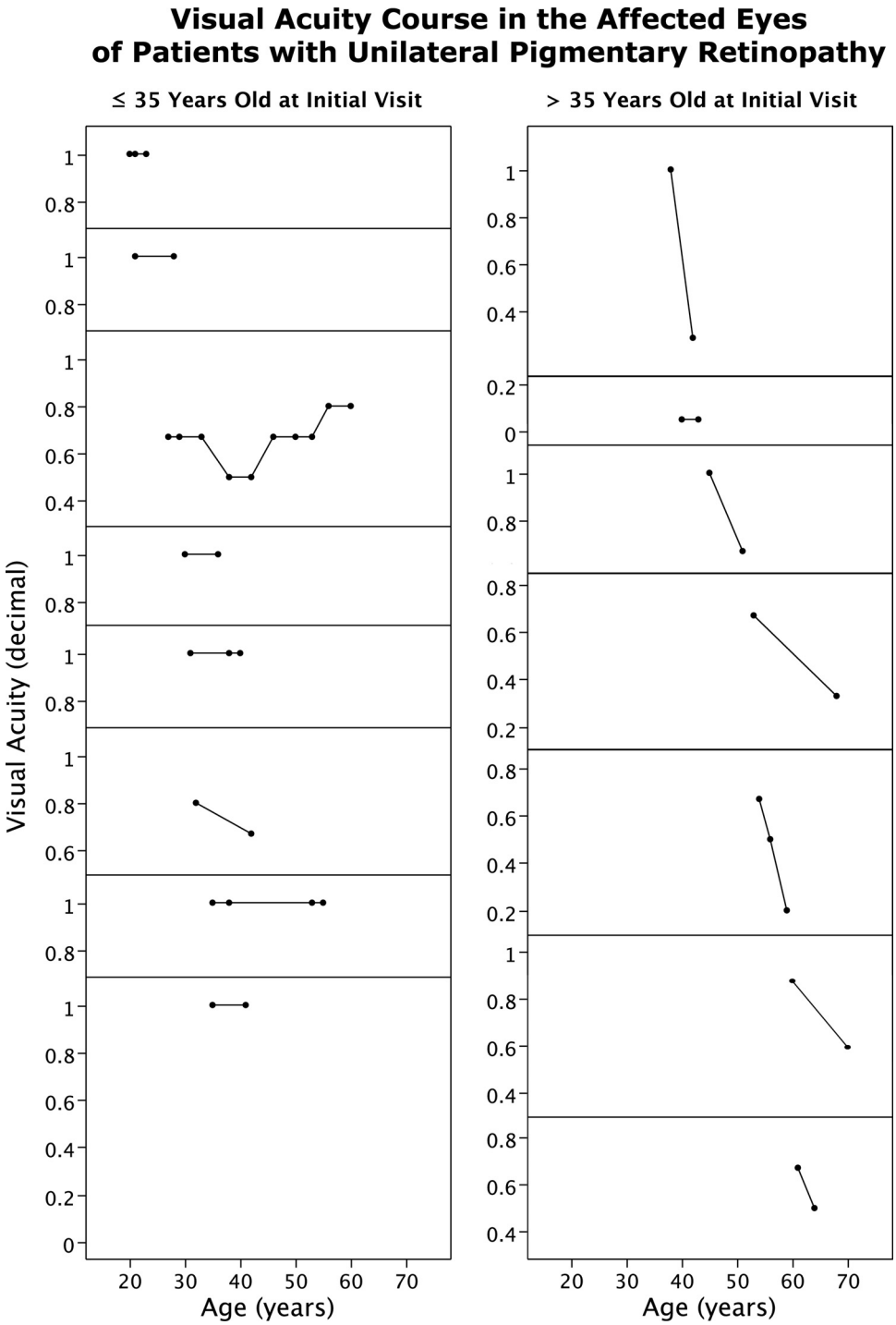


**FIGURE 2.** Plots of Snellen visual acuity as a function of age for the affected eyes of patients with unilateral pigmentary retinopathy, including all visits to illustrate that patients older than 35 years of age at their initial visit were more likely to show visual acuity decline over follow-up than younger patients. Plots in the *left column* and in the *right column* are sorted by increasing age at the initial visit. Patient IDs (from *top* to *bottom*) are 25840, 13391, 687, 5470, 11172, 15711, 25094, and 11345 in the *left column* and 6570, 26346, 14943, 14828, 11250, 19820, and 13209 in the *right column*. Patient 19820 became pseudophakic at follow-up, so the decline in visual acuity in the figure likely underestimates what the decline would have been in the absence of cataract surgery.

Table 2 lists the estimated mean annual exponential rates of change of visual field area and ERG amplitude and the corresponding levels of significance for our cohort with unilateral pigmentary retinopathy. We found a mean annual exponential rate of change in the affected eyes of −4.9% for visual field area, which was highly significant when compared with zero ($P = 0.001$), of −4.7% for ERG amplitude to 0.5-Hz white flashes ($P = 0.0001$), and of −4.6% for ERG amplitude to 30-Hz white flashes ($P = 0.002$). For the fellow normal eyes, we found no significant mean annual rate of change for visual field area, but we did find significant mean annual rates of change of −1.4% for ERG amplitude to 0.5-Hz white flashes ($P < 0.0001$) and −1.2% for ERG amplitude to 30-Hz white flashes ($P = 0.006$). The mean annual rates of decline were faster in affected eyes than those in fellow normal eyes for visual field area ($P = 0.0006$), for ERG amplitude to 0.5-Hz white flashes ($P = 0.003$), and for ERG amplitude to 30-Hz white flashes ($P = 0.03$).

After we determined that disease progression was occurring in affected eyes for visual field and ERG, we evaluated whether initial cone ERG implicit time to 30-Hz flashes (which ranged from 33 to 49 ms) might predict which eyes progressed faster than other eyes. Adding implicit time and its interaction with follow-up in years to the mixed model revealed that each millisecond increase in implicit time was associated with an increased rate of decline of 1.1% for visual field area ($P < 0.0001$), of 1.0% for ERG amplitude to 0.5-Hz flashes ($P < 0.0001$), and of 1.0% for ERG amplitude to 30-Hz flashes ($P = 0.0003$). For clinical application, each affected eye was then assigned a class variable indicating whether the patient's initial implicit time was less than the mean value of 40 ms (0) or more than or equal to this mean value (1). The mean implicit time, which was also the median implicit time, was chosen to balance those with low (0) and high (1) values. This class variable and its interaction with follow-up in years were added to the original mixed model. Table 3 shows that an initial cone ERG implicit time more than or equal to the mean of 40 ms was associated with a faster mean rate of decline of visual field area, of ERG amplitude to 0.5-Hz white flashes, and of ERG amplitude to 30-Hz white flashes ($P < 0.0001$ in all cases).

Figure 2 plots visual acuity for affected eyes as a function of age for all visits. The graphs reveal that 27% of patients (IDs 6570, 11250, 14828, and 19820) experienced a marked decline over follow-up (4 to 15 years), 20% of patients (IDs 13209, 14943, and 15711) had a slight decline over follow-up (3 to 10 years), and 53% of patients (IDs 5470, 687, 11172, 11345, 13391, 25094, 25840, and 26346) showed no decline over follow-up (3 to 33 years). In fact, 40% of patients (IDs 5470, 11172, 11345, 13391, 25094, and 25840) retained a visual acuity of 20/20 over follow-up (3 to 20 years). The graphs also reveal that patients older than 35 years of age at their initial visit were more likely to show progressive loss of visual acuity than younger patients. Logistic regression confirmed a significant positive association between visual acuity loss (comparing the initial to the last measurement) versus age at the initial visit, controlling for initial visual acuity ($P = 0.0004$). If the data for patient 26346 with an initial visual acuity of 20/400 were censored to eliminate a possible floor effect, the analysis showed an even stronger association ($P < 0.0001$).

## Discussion

For the first time, this study shows that the estimated mean annual exponential rates of decline of visual field area and ERG amplitude in the affected eyes of patients with unilateral pigmentary retinopathy were significantly different from zero and significantly faster than the corresponding age-related rates in the fellow normal eyes. Therefore, in addition to presenting with reduced ocular function in the affected eyes, patients with unilateral pigmentary retinopathy can generally expect to lose additional function over time in their affected eyes at a rate that exceeds the normal age-related decline.

Although we observed a large variation in the range of rates of decline in affected eyes, knowledge of the cone ERG implicit time helped to provide a more precise estimate of rates of decline in remaining visual field area and ERG amplitude. For clinical application, initial cone ERG implicit times < 40 ms were associated with a mean annual rate of decline of 1.8% for visual field area, 2.9% for ERG amplitude to 0.5-Hz white flashes, and 2.5% for ERG amplitude to 30-Hz white flashes (see Table 3). Initial cone ERG implicit times that were prolonged to ≥40 ms were associated with a greater mean annual rate of decline of 14% for visual field area, 12% for ERG amplitude to 0.5-Hz white flashes, and 11% for ERG amplitude to 30-Hz white flashes. Thus, the initial cone ERG implicit time of affected eyes enabled us to separate patients with aggressive disease from those showing minimal progression.

Because of the small sample size after censoring to eliminate ceiling and floor effects, it was not possible to estimate the mean annual rate of change of visual acuity in these patients. Nonetheless, we found that the visual acuity of affected eyes was significantly more likely to decrease over follow-up in older patients than in younger patients.

The results provided in this article describe overall tendencies for disease progression in the affected eyes of patients with unilateral pigmentary retinopathy and demonstrate the substantial differences in rates of progression that are associated with differences in initial cone ERG implicit time. The results provide a guideline for advising individual patients of their potential for retaining peripheral retinal function in their affected eye, because those with a cone ERG implicit time < 40 ms have a better prognosis than those with a cone ERG implicit time ≥ 40 ms.

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