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Detecting glaucomatous progression with infrequent visual field testing

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Abstract

Purpose: Previous work has investigated whether a significant regression slope in the first two years for the summary index Mean Deviation (MD) is predictive of rapid (≤−2dB/year) glaucomatous visual field progression. This work assumed six visual fields were obtained as per management guidelines, but in clinical practice commonly only two or three fields are measured. We used simulation methods to investigate how reducing test frequency influences the prediction of rapid visual field progression, along with the influence of including criteria based on regression slope.

Methods: We simulated visual field series (N=100,000) spaced annually in the first two years and then biennially. We calculated positive and negative predictive values (PPV & NPV) for detecting rapid progression, based on a criterion of a significant negative regression slope of any magnitude, or of a magnitude less than a particular limit. We performed a second simulation using test frequency and disease prevalence parameters from a dataset of 255 glaucoma patients from The University of Tokyo Hospital, to check the validity of our method.

Results: Prediction values at two years were slightly less than those obtained using six visual fields. An addition of an appropriate slope based criterion materially improved PPV, with little detrimental effect on NPV. Simulated prediction values for the Tokyo dataset were similar to those determined empirically.

Conclusion: Infrequent visual field testing does not dramatically alter predictive values at two years, but does substantially delay when significant progression may first be detected.

Introduction

Regular examination of the visual field with automated perimetry is an essential tool for monitoring glaucoma patients.[1] It has been suggested that six visual fields are required in the first two years after diagnosis in order to have an adequate power to detect rapid visual field progression (≤−2dB/year, using a linear regression over time of the summary index Mean Deviation, or MD).[2] This finding has been influential in shaping glaucoma management guidelines for how frequently visual field assessments are performed.[1, 3] Although multiple visual field assessments provide appropriate statistical power, it has recently been suggested that

a finding of a significant slope when regressing a patient's MD values over time does not have a high positive predictive value (PPV) for detecting rapid progression.[4] At two years, the PPV for rapid progression was around 0.1: that is, around one in 10 people showing a significant regression slope in the first two years had underlying true rates of progression of –2 dB/year or worse.[4] This lack of a strong prediction reflects, in large part, that the prevalence of rapid visual field progression is low in glaucoma.[5-7] The positive predictive values was also less than 0.5 for a lower – but still troubling – rate of progression of –1 dB/year or worse.[4]

However, there are some limitations with this recent study of the PPV of a significant regression slope.[4] The simulation in the study assumed visual fields were tested at four-monthly intervals in the first two years, in keeping with several current guidelines.[1, 3] However, patients commonly perform only two or three visual field examinations in the first two years in practice.[8] The simulation also demonstrated that using an additional criterion based on the slope of the regression (that is, using a criterion of a significant slope that was also ≤−2dB/year, rather than simply a significant slope alone) increased the PPV. However, only one slope criterion was investigated. It is unknown how the PPV alters as the slope criterion is systematically changed, and whether the PPV might be further improved if a different slope criterion were used. Previous work using pointwise linear regression to detect progression found a non-monotonic relationship between slope criterion and the area under the receiver operating characteristic curve distinguishing progressing from non-progressing fields.[9]

Finally, it would be useful if the general findings of the simulation could be confirmed in a study using empirical data. In keeping with previous works,[2, 10-12] the simulation assumed Gaussian noise in the index MD. As MD represents an average, the central limits theorem would predict its variability should be approximately Gaussian,[13] even though the pointwise sensitivities from which this average is derived are themselves skewed.[14] Whilst there is empirical evidence to suggest this is a reasonable assumption in reliable observers with healthy fields,[13] outlying data points can occur in clinical patients.[15] Furthermore, the simulation assumed that the underlying change in the visual field was linear over time. Although this is commonly assumed to be the case in the literature,[5, 6, 16] some authors have argued that visual field change may be non-linear.[17]

In this paper we perform simulations to examine how the PPV for rapid progression alters when the frequency of visual field testing is reduced from the recommended six visual fields in the first two years to the more typical frequencies seen in clinical settings.[8] We also determine the relationship between the PPV and additional criteria based on the slope of the regression line, to test the hypothesis that PPV can be improved by using a slope criterion other than that explored previously. Finally, we use a subset of data derived from a recently published study,[18] and also used in a large clinical cohort,[5] to test whether the principal relationships seen in our simulations are also seen empirically.

Methods

Simulation Details

Except where otherwise stated, simulation details were as described previously.[4] In brief, we created a longitudinal series of MD values for 100,000 simulated patients whose underlying true progression rates were drawn from a modified hyperbolic secant whose parameters were the average of those fitted to large datasets from Canada, Sweden and the USA.[12] The proportion of people with slopes less than or equal to −2dB/year, −1dB/year and −0.5dB/year were 2.3%, 15.8% and 40.4%, respectively. Each MD value was jittered from its nominal value by applying Gaussian noise with a standard deviation of 1.0 dB, as previously assumed for moderate variability fields.[2, 10, 11] We then applied ordinary least squares linear regression to these MD values over time to estimate both the visual field progression rate and the significance of the regression slope. The criterion for significance was $P < 0.05$.

For our primary simulation, we assumed visual fields were performed annually in the first two years and then biennially after this. Fung *et al*.[8] showed that, across several English hospitals, visual fields were most commonly performed two or three times in the first two years. These values are consistent with patients undergoing approximately annual review initially, with scheduling variability causing some patients' third visits to fall just after, and others just before, the initial two-year window (therefore giving two or three fields in the window, respectively). Assuming biennial review of visual fields after this two-year window (for example, performing perimetry only on every other annual review visit) means that visual fields are performed on

average 0.7 times a year over a 7.2 year window in our simulation. This matches the average 0.7 visual fields per year found in the average 7.2 year follow-up period reported by Fung *et al*.[8] For each simulated patient we created a visual field series of 16 years duration, and performed linear regressions on truncated versions of this series starting from a minimum of the first three fields. It is clear that slope estimates are highly variable with small visual field series,[10] and so in a research setting it is advisable to obtain an extended visual field series before performing regression analyses. However, as has been argued previously,[4] clinicians will likely examine a patient's visual field series at each patient visit, and so examining the performance of regression analyses from the first point they can be performed (that is, three or more fields) is appropriate.

Analyses

Positive and Negative Predictive Values: We calculated positive and negative predictive values (PPV & NPV) in two ways. For our main analyses (represented by symbols in the appropriate figures), a visual field series was judged as having progressed at a particular visit if the criteria of slope significance and slope magnitude were met at that visit and/or at any visit prior to that (from visit three onwards). This was done to be more consistent with what might be done clinically (assessing for progression at each visit) rather than in a controlled study (for example, assessing for progression only after a predetermined time). As a secondary analysis, we calculated predictive values based on an assessment of progression made only at the specified visit.

Empirical Investigation

We obtained 314 glaucoma patients' visual field reports (24-2 or 30-2, Humphrey Field Analyzer II (HFA) (www.zeiss.com) from The University of Tokyo. Classification of patients, and ethical approval for the study was identical to that reported for the Japanese Archive of Multicentral Databases in Glaucoma.[5] We commenced with 7,861 visual field reports, to which the following eligibility criteria were applied:

1. Fixation loss <20% and false positive <15% (excluded 550 reports). False negative was not used as an exclusion criterion, following the manufacturer's recommendation.

2. Only one eye per subject, selected at random if both eyes were eligible (excluded 2,797 reports of other eye).

3. Minimum of six years follow up period (excluded 39 Subjects, 417 reports).

4. Minimum of 11 visual field reports per patient (excluded 20 subjects, 200 reports).

Visual field series from 255 patients met these criteria. Each patient's true progression rate was taken as the slope of the ordinary least squares linear regression of his or her entire visual field series, including the baseline visual field. Rate estimates were calculated for truncated visual field series (i.e. the first two, three or four years), and the positive and negative predictive values calculated for a significant negative slope in this truncated regression predicting a true progression rate of ≤ -1dB/year. We did not determine predictive values for rates ≤ -2dB/year owing to the absence of any such rates in the group. We determined the variability of these predictive values by a bootstrap procedure, where PPV and NPV was calculated for each of 100,000 new groups of 255 patients created by sampling, with replacement, from the original 255 patient group.

Results

Simulation Results

Figure 1 shows the influence of the length of the visual field series on the ability to detect glaucomatous visual field progression of different magnitudes, using a criterion of a significant negative regression slope. The PPV is low for detecting rapid progression (top panel, filled squares), peaking at 0.11 after four years. For comparison, results are also shown for when visual fields are done at four-monthly intervals (stars), consistent with published guidelines[1, 3] and as reported previously.[4] At two years, the PPV for detecting rapid progression is slightly poorer for infrequent fields, compared with more frequency testing (0.42 versus 0.37). For all conditions, there is a modest difference between whether predictive values were based on a significant

regression slope either at the time in question (short dashed lines) or at that time and/or at any preceding time (symbols). The NPV for rapid progression is high even from two years, indicating that if a significant negative regression slope is not found, rapid visual field progression is unlikely to be present. These NPV values are, however, still reduced compared to those obtained with four-monthly testing, as published previously (stars).[4] The PPV for a less rapid progression rate of −1 dB/year (unfilled squares), as determined with infrequent testing, is reduced at two years compared to the PPV obtained with four-monthly testing. The PPV with infrequent testing does, however, peak at a slightly higher value at four years. NPV is reduced, however. Re-running our simulation found the cumulative PPV and NPVs reported in *Figure 1* shifted by an average of 0.0014 and 0.0010, respectively, with no value shifting more than 0.011.

Figure 2 shows how predictive values alter as a function when an additional criterion based on the slope magnitude is used, rather than simply the significance of the regression slope alone. At two years (left panels), the PPV increases systematically as slope criterion increases, and exceeds 0.5 when an additional criterion of ≤ −2dB/year is used. In contrast, an additional slope criterion has little influence on the NPV for rapid progression. A similar result is found at four years (right panels), although the rise in PPV is accelerated. This acceleration continues for longer series (*Figure 3*, six and eight years), allowing a PPV greater than 0.5 to be achieved using a lower slope criterion of ≤ −1.5dB/year. Although there is a clear drop in the NPV for detecting either any (unfilled circles) or less-than-rapid (filled circles and unfilled squares) progression as an additional slope criterion increases, the NPV for rapid progression remains above 0.98 (filled squares). To visualise more readily how predictive values alter with the length of follow-up, *Figure 4* replots a subset of data from *Figure 2* and *Figure 3* for detecting either any significant progression (left panels) or progression ≤ −2dB/year.

Empirical Results

Of our group of 255 subjects (132 male, 123 female), 97 (38%) had primary open angle glaucoma and 158 (62%) had normal-tension glaucoma. *Figure 5* gives the median time of each visual field measurement. Testing was regularly spaced and reasonably frequent, with four tests performed in the first two years. The prevalence of progression ≤ −1dB/year was 7.1% (*Figure 6*, upper panel). The lower panel of *Figure 6* gives the cumulative empirical predictive values for

detecting progression rates ≤ −1dB/year based on a criterion of a significant negative regression slope in the visual field series truncated to three or four years (unfilled symbols). PPV and NPV at two years are not shown as no person with progression ≤−1dB/year had a significant regression slope at this time in our sample. A simulation of the empirical results was performed, using the median standard deviation of the empirical MD data about the regression slopes (= 0.98) and visual field spacing based on the median values reported in *Figure 5*. The results (cumulative and non-cumulative, filled symbols and short dashed lines respectively) typically fall within or close to the 95% bootstrap limits about the empirical data. Our simulation results do, however, slightly overestimate negative predictive values.

Discussion

Our results show that using infrequent visual field data (annual review in the first two years, and then biennially) produced a modest reduction in PPV for detecting rapid visual field progression compared to more frequent testing (four-monthly testing), when considered at an equivalent time of two years. PPV increases monotonically as the magnitude of an additional criterion on the regression slope increases (*Figure 2* and *Figure 3*), and is close to 0.6 after two years when a strict criterion of ≤−2.5dB/year is used. NPV was also reduced by infrequent field testing at two years. This result is consistent with the idea that a visual field series with a true, underlying rate of progression of ≤−2dB/year may return a non-significant regression slope with only three fields (as with infrequent testing). Importantly, our simulation produces results similar to those obtained from an analysis of clinical data (*Figure 6*), which strengthens the validity of our simulation approach. Agreement was not perfect, however, which is not unexpected given that our simulation represents a simplified model of how visual field progression occurs. One potential reason for a deviation between our simulation and the Tokyo data could be that visual field progression may not be perfectly linear.[17] Non-linearities might also be expected to be more prominent in clinical – rather than in study - data where patients may have ongoing alterations made to their glaucoma management. The likelihood of such management changes might be expected to increase in those patients showing signs of rapidly progressing disease. Nonetheless, a recent study found that there was no merit in using non-linear regression methods to predict future visual field progression in clinical data, compared with linear regression.[19]

It should be noted that NPVs (and, in some circumstances, PPVs) are higher for a given number of visual fields when infrequent testing is performed (*Figure 1*). As fields are more widely spaced, visual field damage progresses more after a fixed number of fields with infrequent testing and so the signal to be detected – compared to the noise inherent in perimetry - is increased. Because of this, infrequent visual fields will typically contain more information per visual field as to whether progression is present, and the likelihood of finding a significant regression slope is increased when progression is present. This will lead to the improvement of NPV given its monotonic relationship with time (*Figure 1*). However, PPV may not always increase given its non-monotonic relationship; with sufficient time, even very slowly progressing fields will return significant regression slopes, and so the present of a significant slope alone becomes a less reliable indicator that rapid progression is present.

Although we find that PPV at any given time after two years is not dramatically altered by the sort of infrequent testing that may be seen in some clinical practice settings,[8] there are other disadvantages that may arise. With the infrequent testing modelled here, regression analysis cannot be performed until two years, thereby significantly delaying when PPV and NPV can be first formally assessed. We believe this represents one of the principal disadvantages of infrequent visual field testing. In contrast, with six fields obtained in the first year, regression analyses can be performed in under one year. With home monitoring, a further improvement in the early detection of rapid progression of the visual field may be achieved.[20] In addition, accurately determining the progression rate – rather than simply that statistically significant progression is present - is challenging, and has been estimated to take around five years given a reasonable frequency of visual field testing.[10] With infrequent testing, the confidence intervals surrounding slope estimates will necessarily be larger and the time needed to accurately quantify rates thereby increased.

The distribution of visual field progression rates in our Tokyo dataset is asymmetric (*Figure 6*), with a larger tail for negative slopes that is characteristic of distributions compared elsewhere.[12] Of interest is that the median time to reach six visual fields is around three years (*Figure 6*). This indicates a closer following of visual fields compared to that seen in data from England, where the median time to achieve six visual fields was approximately five years.[8] Variability in follow-up is also reduced, with the time to receive six visual fields taking between ~3.5 to 10 years in

England (tenth and ninetieth percentiles), compared with ~ two to four years in Tokyo dataset. Part of this decreased variability may be due to our current dataset being derived from a single hospital setting, whereas that of Fung, *et al*.[8] was drawn from six hospitals. Of note is that both of these studies were drawn from clinical, rather than study, records and so presumably provide a measure of the frequency of visual field investigations performed by hospital-based clinicians in both regions.

Our analyses were performed using a linear regression of the summary index MD, which has been shown to be more sensitive to change than similar regressions using the global indices Visual Field Index (VFI) or Pattern Standard Deviation.[21] Furthermore, although regression of VFI are designed to be interpretively easy, irregularities in VFI-based metrics can occur for both low rates of change[22] and for visual fields of MD <–20 dB.[23] Despite these differences, broadly similar results to ours may be anticipated used the VFI, given VFI progression rates and MD rates are closely related.[22]

In summary, infrequent visual field testing does not dramatically impair predictive values of a significant regression slope for detecting rapid visual field progression at two years, compared with more frequent testing. Selecting an appropriate additional criterion for the slope of the regression can materially increase positive predictive values, with only limited detrimental effects on negative predictive values. Infrequent testing does, however, significantly delay the time at which predictive values can be first calculated, and delays the ability to rule out rapid visual field progression by over a year when compared to when testing frequency guidelines are adhered to. Given that the identification and management of patients with rapidly progressing glaucoma represents a pressing clinical challenge, such delays may not be unacceptable, particularly in those patients with significant risk factors for rapid visual field loss.

Figure 1: Positive predictive values (PPV) and negative predictive values (NPV) for visual field progression worse than, or equal to, a particular rate, as a function of time after diagnosis. Symbols show when visual fields were judged to be progressing at a particular time if a significant negative regression slope was found at that time, and/or at any preceding time. Short dashed lines show when progression is defined as a significant negative regression slope only at the time in question. For comparison, stars show PPV and NPV values for when visual fields are

done at four-month intervals in the first two years, and then annually (filled stars = ≤−1.0 dB/yr; unfilled stars = ≤−2.0 dB/yr) as previously published.[4] We provide lines linking our data points purely to aid visual grouping, and not to imply that our necessarily discrete functions are continuous.

Figure 2: PPV and NPV for significant visual field progression worse than, or equal to, a particular rate, as a function an addition criterion based on slope. For example, in the top left panel, the filled square third from the right gives the PPV for detecting a true underlying visual field progression of ≤−2.0 dB/yr, assuming a criterion of a significant regression of slope ≤−1.0 dB/yr. In this example, 54% of visual field series with significant regression slopes ≤−1.0 dB/yr would be expected to have a true underlying progression rate of ≤−2.0 dB/yr. Data for assessments after two or four years are shown in the left and right panels, respectively. Other details are as given in *Figure 1*.

Figure 3: PPV and NPV for visual field progression worse than, or equal to, a particular rate, as a function slope criterion, assessed after six or eight years (left and right panels, respectively). Other details are as given in *Figure 1*.

Figure 4: Replotted data from *Figure 2*and *Figure 3*, showing PPV and NPV for detecting any progression (left panels) or progression of ≤−2dB/year (right panels) as a function of time, for various different slope criteria. Predictive values were calculated based on if visual fields were judged to be progressing at a particular time, and/or at any preceding time.

Figure 5: The median time from baseline (= visit 1) for the first 10 follow-up visits. Error bars give the tenth and ninetieth percentiles.

Figure 6: Distribution of visual field progression rates for the Tokyo dataset (top panel), along with the positive and negative predictive values for detecting progression rates of ≤−1dB/year.

Table 1: Number of participants with a particular number of follow-up visits, for the three different truncated series used in our empirical study.

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References

1. NHMRC (National Health and Medical Research Council). NHMRC Guidelines for the screening, prognosis, diagnosis, management and prevention of glaucoma 2010. Canberra, ACT: National Health and Medical Research Council; 2010.

2. Chauhan BC, Garway-Heath DF & Goñi FJ, *et al*. Practical recommendations for measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2008; 92: 569-573.

3. European Glaucoma Society. Terminology and guidelines for glaucoma. 4th Edition ed. Savona, Italy: PubliComm; 2014.

4. Anderson AJ. Significant glaucomatous visual field progression in the first two years: what does it mean? *Transl Vis Sci Technol* 2016; 5:1.

5. Fujino Y, Asaoka R & Murata H, *et al*. Evaluation of glaucoma progression in large-scale clinical data: the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG). *Invest Ophthalmol Vis Sci* 2016; 57: 2012-2020.

6. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT & Artes PH. Rates of glaucomatous visual field change in a large clinical population. *Invest Ophthalmol Vis Sci* 2014; 55: 4135-4143.

7. Heijl A, Buchholz P, Norrgren G & Bengtsson B. Rates of visual field progression in clinical glaucoma care. *Acta Ophthalmol* 2013; 91: 406-412.

8. Fung SS, Lerner C, Russell RA, Malik R & Crabb DP. Are practical recommendations practised? A national multi-centre cross-sectional study on frequency of visual field testing in glaucoma. *Br J Ophthalmol* 2013; 97: 843-847.

9. Kummet CM, Zamba KD, Doyle CK, Johnson CA & Wall M. Refinement of pointwise linear regression criteria for determining glaucoma progression. *Invest Ophthalmol Vis Sci* 2013; 54: 6234-6241.

10. Jansonius NM. On the accuracy of measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2010; 94: 1404-1405.

11. Anderson AJ & Johnson CA. How useful is population data for informing visual field progression rate estimation? *Invest Ophthalmol Vis Sci* 2013; 54: 2198-2206.

12. Anderson AJ. Estimating the true distribution of visual field progression rates in glaucoma. *Invest Ophthalmol Vis Sci* 2015; 56: 1603-1608.

13. Anderson AJ, Cheng ACY, Lau S, Le-Pham A, Liu V & Rahman F. The retest distribution of the visual field summary index mean deviation is close to normal. *Ophthalmic Physiol Opt* 2016; 36: 558-565.

14. Heijl A, Lindgren G & Olsson J. Normal variability of static perimetric threshold values across the central visual field. *Arch Ophthalmol* 1987; 105: 1544-1549.

15. Bryan SR, Eilers PHC, Lesaffre EMEH, Lemij HG & Vermeer KA. Global visit effects in point-wise longitudinal modeling of glaucomatous visual fields. *Invest Ophthalmol Vis Sci* 2015; 56: 4283-4289.

16. Heijl A, Bengtsson B, Hyman L, Leske MC & Group EMGT. Natural history of open-angle glaucoma. *Ophthalmology* 2009; 116: 2271-2276.

17. Pathak M, Demirel S & Gardiner SK. Nonlinear, multilevel mixed-effects approach for modeling longitudinal standard automated perimetry data in glaucoma. *Invest Ophthalmol Vis Sci* 2013; 54: 5505-5513.

18. Murata H, Araie M & Asaoka R. A new approach to measure visual field progression in glaucoma patients using variational bayes linear regression. *Invest Ophthalmol Vis Sci* 2014; 55: 8386-8392.

19. Taketani Y, Murata H, Fujino Y, Mayama C & Asaoka R. How many visual fields are required to precisely predict future test results in glaucoma patients when using different trend analyses? *Invest Ophthalmol Vis Sci* 2015; 56: 4076-4082.

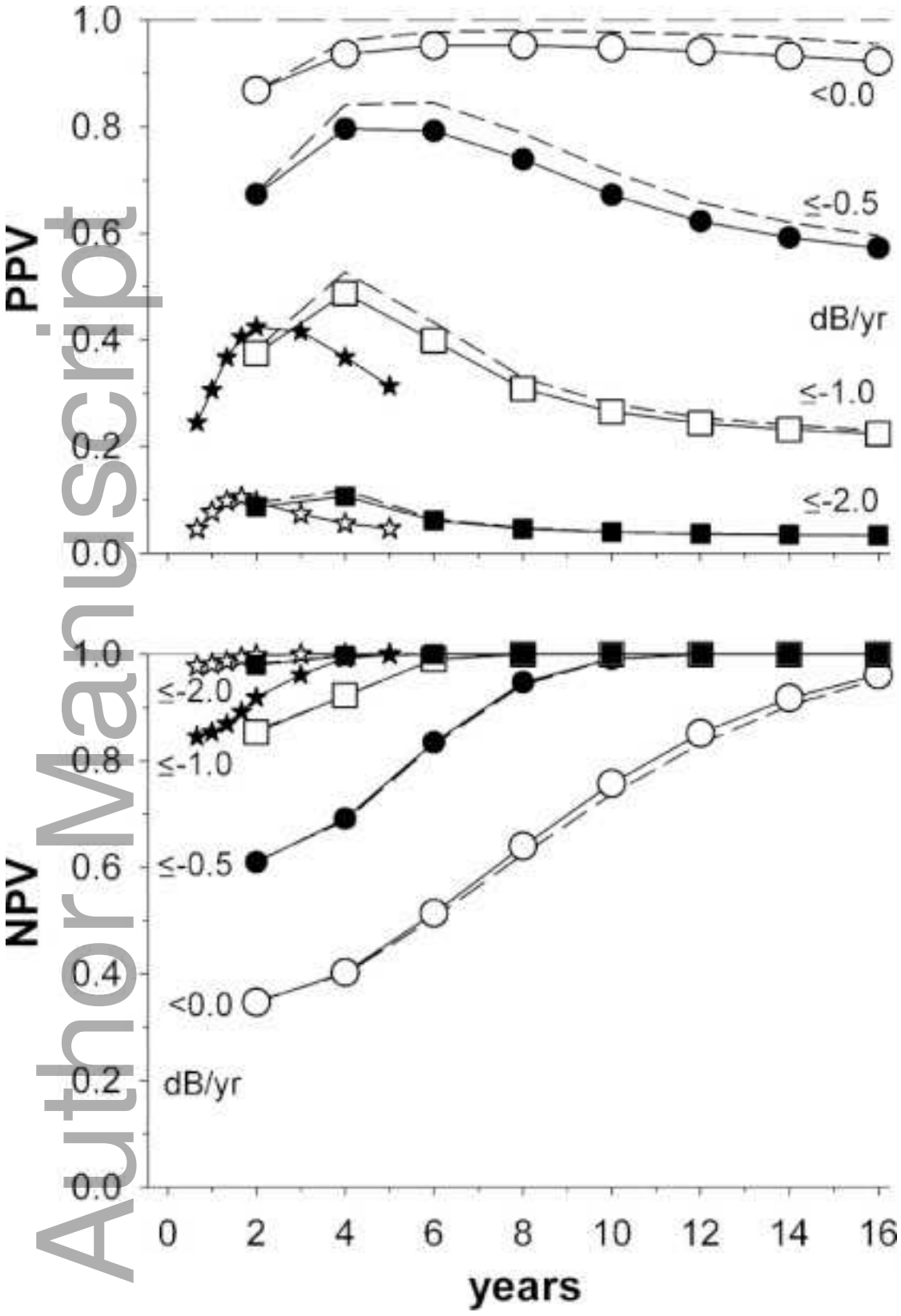
20. Anderson AJ, Bedggood PA, Kong GYX, Martin KR & Vingrys AJ. Can home monitoring allow earlier detection of rapid visual field progression in glaucoma? *Ophthalmology* 2017; 124: 1735-1742.

21. Gardiner SK & Demirel S. Detecting change using standard global perimetric indices in glaucoma. *Am J Ophthalmol* 2017; 176: 148-156.

22. Artes PH, O'Leary N & Hutchison DM, *et al*. Properties of the statpac visual field index. *Invest Ophthalmol Vis Sci* 2011; 52: 4030-4038.

23. Rao HL, Senthil S, Choudhari NS, Mandal AK & Garudadri CS. Behavior of Visual Field Index in advanced glaucoma. *Invest Ophthalmol Vis Sci* 2013; 54: 307-312.

No of visits	Duration of Follow-up		
	2 years	**3 years**	**4 years**
1	4	1	0
2	14	0	0
3	47	10	2
4	124	29	3
5	48	71	24
≥ 6	18	144	226
Total	**255**	**255**	**255**



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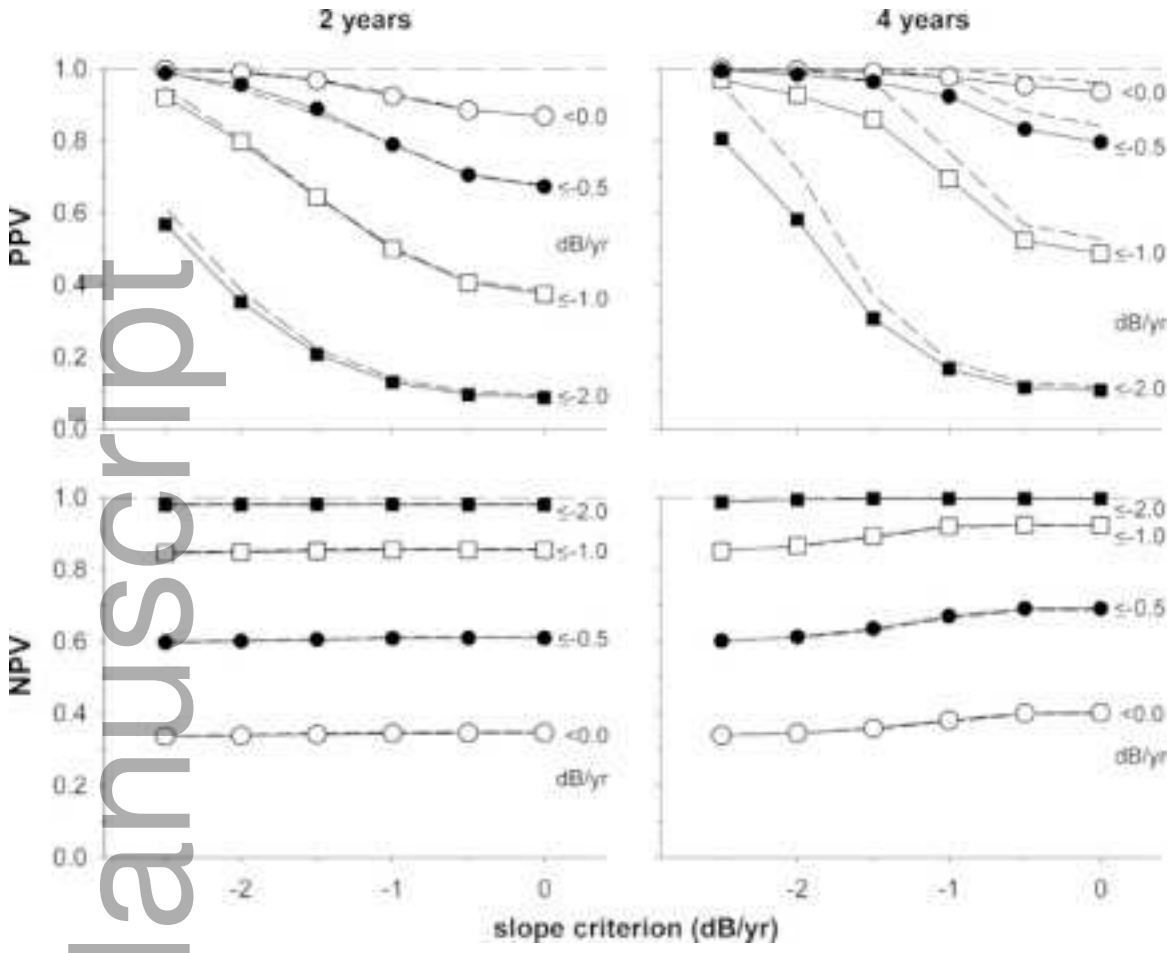

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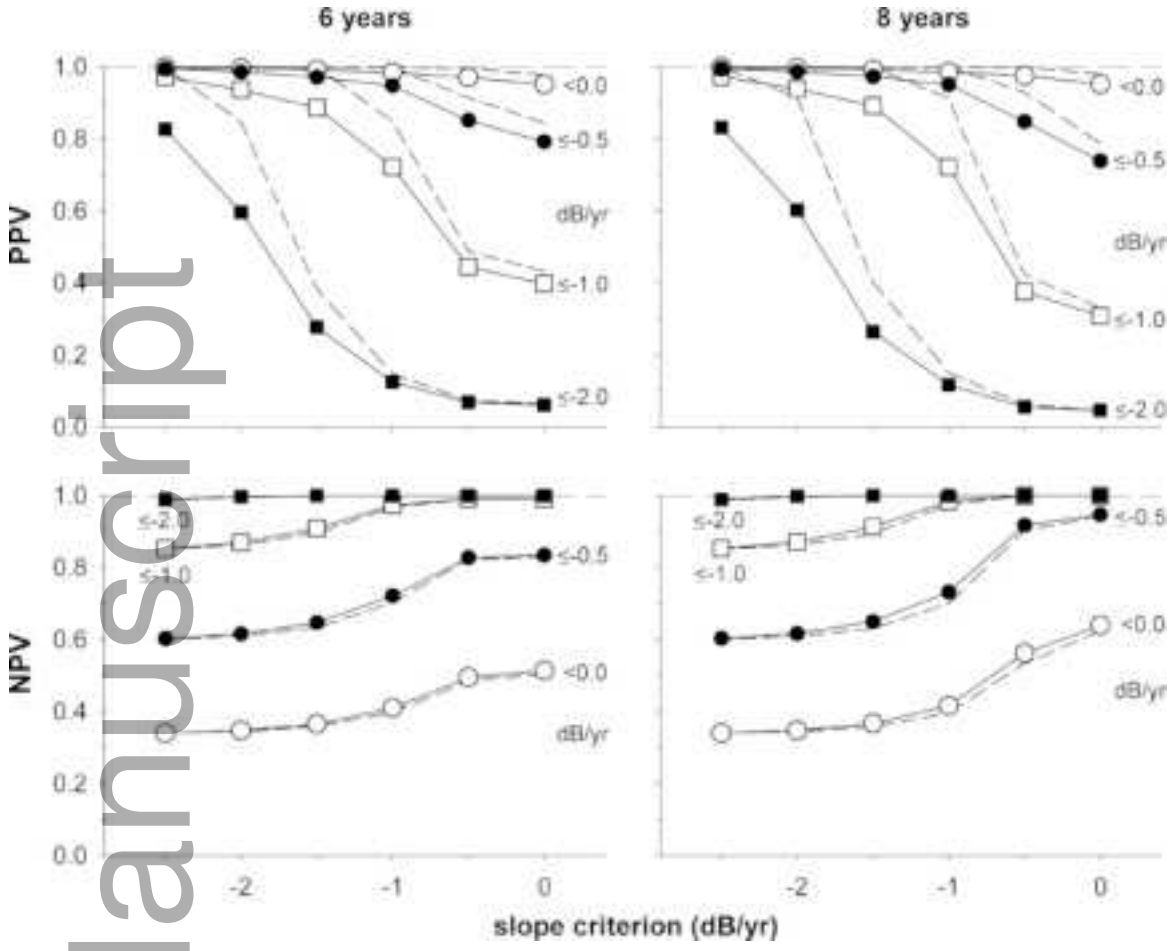

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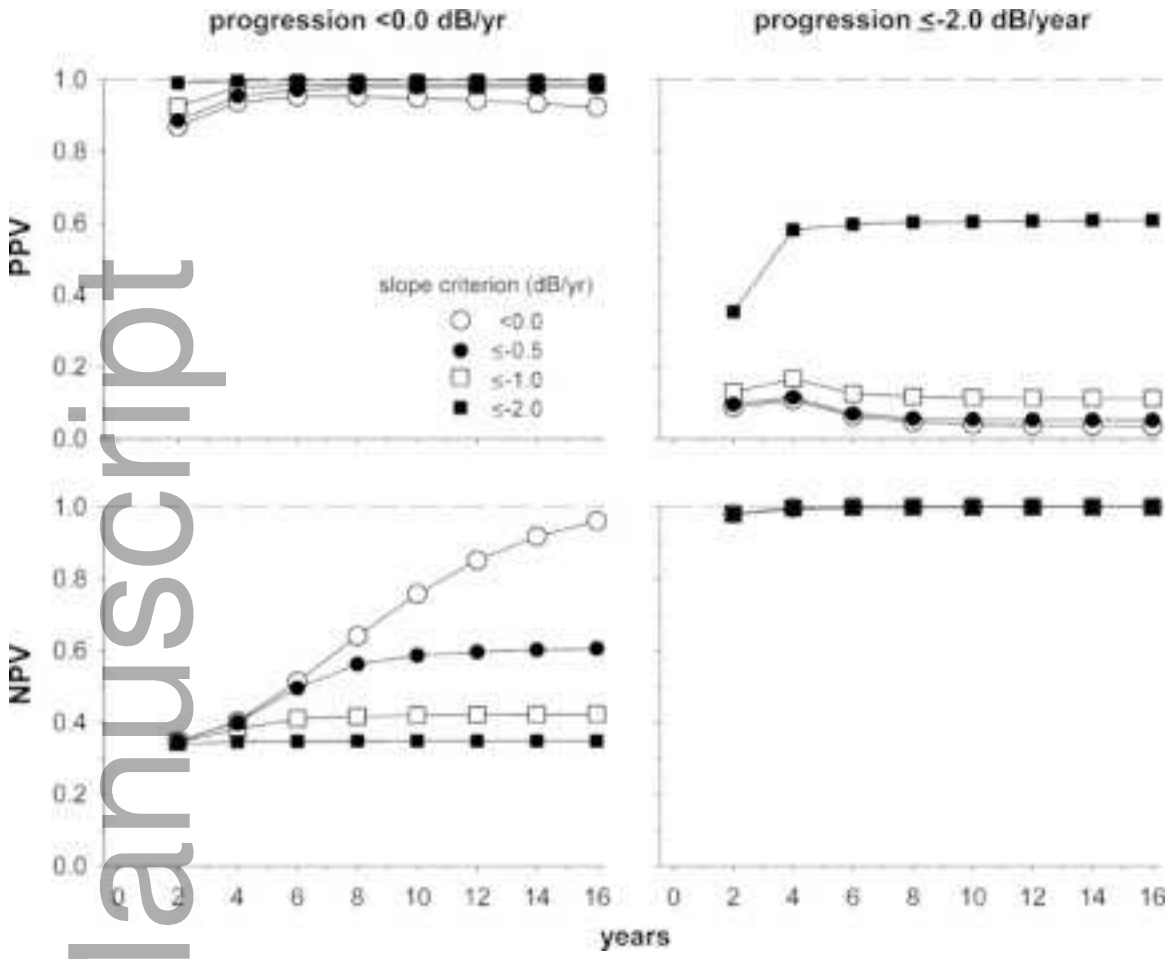

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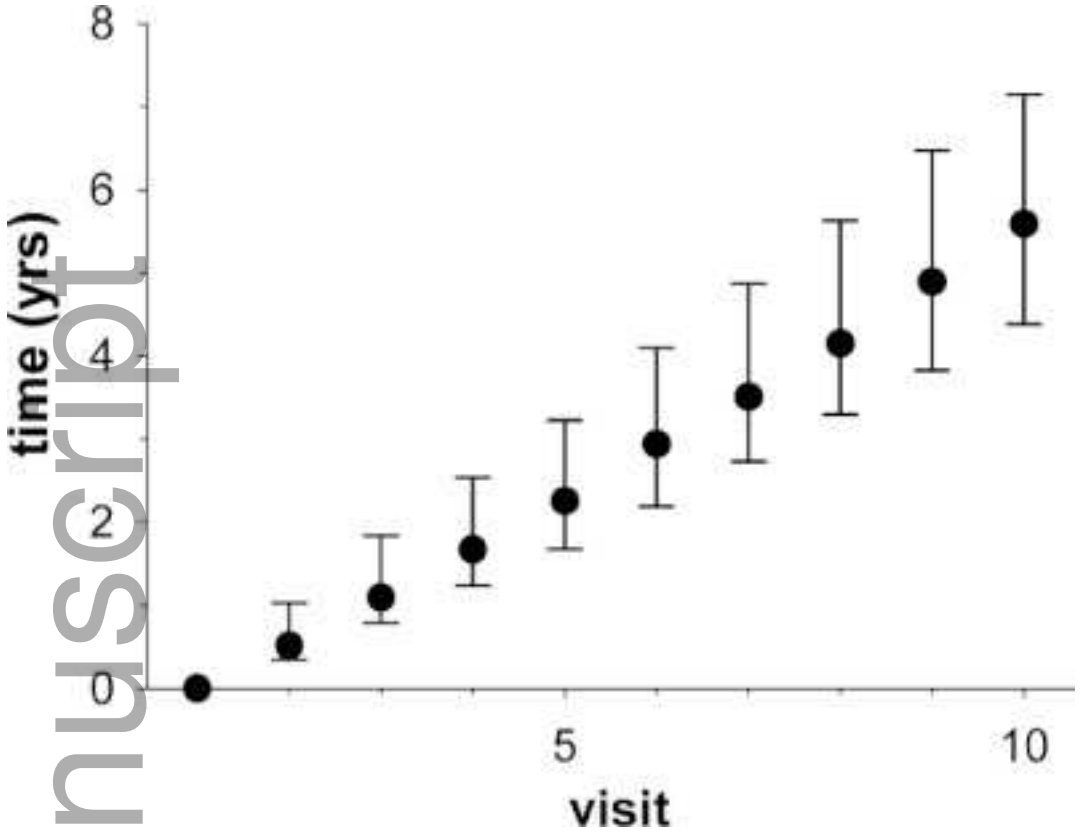

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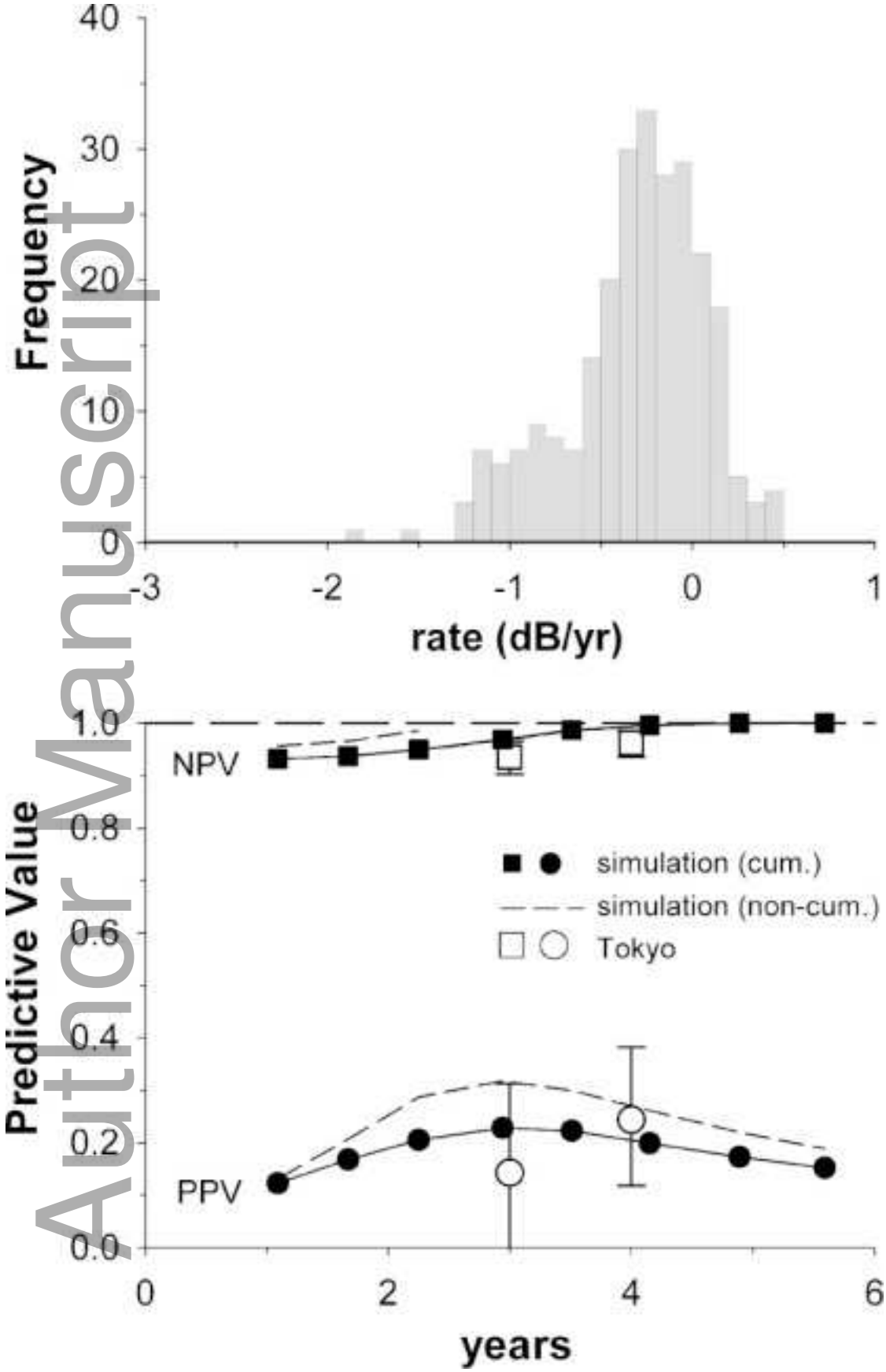

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