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# Comparing 10-2 and 24-2 Visual Fields for Detecting Progressive Central Visual Loss in Glaucoma Eyes with Early Central Abnormalities

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## Abstract

**Purpose:** To compare the ability of 10-2 visual field tests and central 12 locations of the 24-2 tests (C24-2) to detect central visual field progression in glaucoma eyes with early central visual field abnormalities.

**Design:** Observational cohort study

**Participants:** Three-hundred eyes of 180 participants with glaucoma or ocular hypertension

**Methods:** Participants with both 10-2 and 24-2 tests performed on ≥3 visits over ≥1-year period were included to estimate the longitudinal variability of 10-2 and C24-2 visual field mean deviation (MD). The variability estimates were then used to reconstruct real-world visual field results by computer simulations, in a scenario where eyes had a baseline 10-2 and C24-2 MD was −2 dB and exhibited various rates of change (−0.25, −0.50, −0.75 and −1.00 dB/year), and the time to detect these changes were evaluated using trend-based analyses.

**Main Outcome Measures:** Time required to detect progression

**Results:** Overall, the time to detect central visual field progression was reduced by 7-9% using the 10-2 compared to C24-2 MD values, equivalent to a total reduction of 0.1-0.3 dB lost. For example, 90% of eyes with a central 10-2 or C24-2 MD loss of −0.50 dB/year would be detected

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after 5.0 and 5.5 years of semi-annual testing respectively, or after 3.4 and 3.7 years respectively for eyes with a −1.00 dB/year loss.

**Conclusions:** Trend-based analyses using 10-2 MD resulted in a mild reduction (7-9%) in the time to detect central visual field progression compared to C24-2 MD in glaucoma eyes with early central visual field abnormalities. Further studies are needed to determine whether other progression analyses can better exploit the increased sampling of 10-2 tests. These findings provide evidence-based guidance on the potential value-add of 10-2 testing in the clinical management of glaucoma patients.

## Précis:

This study compared 10-2 and 24-2 tests for detecting progressive central visual field changes using computer simulations when assuming that eyes had early central abnormalities, providing important evidence-based guidance on the value-add of 10-2 tests.

### Keywords

Glaucoma; 10-2; Progression; Visual Field

## INTRODUCTION

The characterization of the extent and rate of visual field loss is central in the clinical management of glaucoma, providing an understanding about both the current state and future risk of functional disability.[1,2] In particular, the central visual field plays an important role in daily functioning, and recent studies have demonstrated that central visual field loss is closely related to self-reported quality of life in individuals with glaucoma.[3-5] An accumulating body of evidence in recent years have provided an increased appreciation about both the nature and prevalence of glaucomatous macular damage that can result in such central visual field loss.[6] Importantly, although the macula represents only a small proportion of the entire retina, it contains the highest density of retinal ganglion cells, that can become lost in glaucoma.[6] Despite the recognition of its importance, there is little information available pertaining to the optimal methods for detecting progressive central visual field loss.

Recent studies have suggested that performing a test with an increased sampling density of the central visual field – such as with the 10-2 strategy on the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA) – could improve the detection of progressive visual field loss in this region compared to more conventional stimulus patterns (e.g. the 24-2 strategy).[7,8] One study suggested this on the basis that a substantially greater number of glaucoma eyes showed central visual progression on the 10-2 test compared to the spatially corresponding central locations on the 24-2 test. However, visual field progression was simply considered to have occurred when a single location showed a statistically significant negative slope that exceeded −1 dB/year using point-wise linear regression (PLR) analysis. Given that the sampling density of the 10-2 test is nearly six-fold that of the 24-2 central locations, it is unsurprising that this analysis would flag more eyes as having progressed merely by chance. This would result in a substantially higher false-positive rate with the

10-2 test than the 24-2 test, making the comparison of the two methods non-equivalent. Another study suggested that the 10-2 test could allow progressive central visual field loss to be more effectively captured than the 24-2 test in eyes with advanced glaucoma.[8] This was based on the observation that the rate of visual field mean deviation (MD) change for the 10-2 test was significantly more negative than that from all the test locations of the 24-2 test. However, this is also unsurprising because visual field MD from the entire 24-2 test for eyes with advanced glaucoma – often with relative central visual field preservation – averages measurements from scotomatous non-central regions (that would thus be non-progressive), which can thus reduce the overall rate of change that could be occurring primarily in the central region.[7] The comparison of the 10-2 and 24-2 tests for detecting progressive central visual field loss is therefore also non-equivalent in this case.

In order to better understand the value-add of 10-2 testing for detecting central visual field progression, it should be compared with the measurements obtained from the central test locations of the 24-2 tests, and specificities of the two methods should be matched. This study thus sought to perform such an equivalent comparison to provide evidence-based guidance on the role of 10-2 visual field testing in the clinical management of glaucoma.

## METHODS

This study included participants that were enrolled in two prospective longitudinal observational study of optic nerve structure and visual function in eyes with glaucoma – the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES).[9] These studies were conducted at three sites: Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego, Edward S. Harkness Eye Institute at Columbia University Medical Center (site formerly located at New York Eye and Ear Infirmary), and the Department of Ophthalmology, University of Alabama, Birmingham. Institutional review board approvals were obtained from all study sites involved in this study, and it was conducted in adherence with the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act, and written informed consent was obtained from all participants.

The testing procedures of these studies have been described in detail previously.[9] Briefly, all participants underwent a comprehensive ophthalmologic evaluation that included an annual review of their medical history, best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure and pachymetry measurements, dilated fundus examination and optic disc stereophotography. In this study, all participants included also performed visual field testing using the Swedish Interactive Thresholding Algorithm Standard 24-2 and 10-2 strategy on the Humphrey Field Analyzer II-i (Carl Zeiss Meditec, Dublin, CA) approximately every six-months.

This study included eyes with glaucoma defined on the basis of masked grading of the optic nerve appearance on stereophotographs as described in detail previously,[9] and also eyes with ocular hypertension, defined as having an intraocular pressure of 22 mm Hg or greater. All participants were also required to have open angles on gonioscopy, a best-corrected visual acuity of 20/40 or better and be older than 18 years of age. Participants were also excluded if

they had any other ocular or systemic disease that could affect the optic nerve or the visual field.

## Visual Field Testing

Both the 10-2 and 24-2 visual field tests were considered unreliable and thus excluded if there was > 33% fixation losses or false negative errors (with the exception for false negative errors when the visual field mean deviation [MD] was less than −12 dB), or if there was > 15% false positive errors. Experienced graders at the University of California, San Diego (UCSD) Visual Field Assessment Center (VisFACT) reviewed all the results, excluding tests with artifacts including eyelid or rim artifacts, fatigue or learning effects, inappropriate fixation, for evidence that the visual field results were caused by a disease other than glaucoma (e.g. homonymous hemianopia) or inattention.[10]

In this study, only eyes that had at least three visits over a minimum of a 1-year period where the 10-2 and 24-2 visual field tests were performed on the same day and at least one 24-2 test prior to the first visit where both the 10-2 and 24-2 tests were first performed (i.e. having previous experience with perimetry testing) were included. To compare the ability of the 10-2 and 24-2 tests at detecting central visual field progression, the MD of the central 12 locations of the 24-2 visual field test (C24-2) was calculated due to its close spatial correspondence with the area tested by the 10-2, as shown in Figure 1.

Note that MD on the HFA is conventionally calculated as a weighted average of the total deviation (*TD*) values, being the difference between the measured sensitivity from age-expected values[11] as follows, where $n$ represents the total number of test locations and $w$ indicates the weighting factor at each individual location ($i$):

$$MD = \frac{1}{n} \cdot \sum_{i=1}^{n} (TD_i \times w_i)$$

However, since the weighting applied to the 10-2 and C24-2 by the device manufacturers differ, derived MD values will not be equivalent. To enable a direct comparison between the 10-2 and 24-2, the weights were omitted and thus MD was calculated simply as an arithmetic average of the *TD* values in this study. Calculating MD using the methods specified by the device manufacturers did not alter the conclusions of this study (data not shown).

## Computer Simulations

The methods used to simulate “real-world” visual field results was performed in a similar manner as described in previous studies.[12-14] As an overview, the clinical cohort included in this study were used to provide estimates of the variability of the 10-2 and C24-2 MD over time, and these variability estimates were then used in computer simulations to compare the time to detect various rates of central visual field loss

To obtain the estimates of measurement variability, ordinary least squares linear regressions were fitted to the 10-2 and C24-2 MD values over time for each eye. The difference between

the fitted values and actual measurements were obtained (termed residuals), and then grouped into 1-dB bins according to the fitted values so that they could be used in the computer simulations (details further below). The distribution of the residuals at three representative fitted sensitivity bins are shown in Figure 2.

These estimates of measurement variability were then used to reconstruct “real-world” visual field results as illustrated in Figure 3. To achieve this, the “true” 10-2 or C24-2 MD values were first determined by specifying the baseline level of visual field loss and the rate of change over time. For example, an eye assumed to have a baseline MD of −2 dB and progressing at −0.5 dB a year would have MD values of −2, −2.5, −3, −3.5 and −4 and −4.5 dB at baseline, 1, 2, 3, 4 and 5 years respectively. As measurement variability has been shown to vary with severity of visual field damage, “real-world” visual field results were simulated by randomly adding the 10-2 and C24-2 MD residuals (being the variability estimates) from the fitted sensitivity bin corresponding to the simulated true MD at each time point.

Visual field progression was then evaluated in each sequence of simulated results based on global trend-based analysis of the 10-2 and C24-2 MD values. Progression was considered to have occurred when a statistically significant negative MD slope is present on two consecutive visits, as illustrated in Figure 3.

Computer simulations were first used to find a criterion that matched the specificities of the trend-based analysis of the 10-2 and C24-2 MD values after 5-years of follow-up. This was achieved by generating 10,000 sequences of visual field tests where the “true” 10-2 and C24-2 MD at baseline were assumed to be −2 dB (representing an early, but clinically important degree of central visual field loss), with a rate of change of 0 dB/year (representing non-progression). The visual field testing paradigm involved having two tests at baseline, and semi-annual testing over a 5-year follow-up period. The *P*-value for the statistical significance of the MD slope that resulted in only 5% progression rate by the end of the 5-year follow-up period (or 95% specificity) for the 10-2 and C24-2 methods were then determined to be P = 0.057 and P = 0.059 respectively, and these values were used in subsequent simulations.

Computer simulations were then used to evaluate the time required to detect central visual field progression for various true rates of 10-2 and C24-2 MD change over time, visual field simulations were also performed as described above. The true baseline MD was specified as −2 dB, and we evaluated true MD rates of change of −0.25, −0.50, −0.75 and −1.00 dB/year. The testing paradigm also included two baseline tests followed by semi-annual testing, and visual field progression was defined when a statistically significant negative MD slope was detected at two consecutive visits, based on the *P*-value that provided 95% specificity for the 10-2 and C24-2 methods. An example of how measurement variability was simulated for an eye specified as progressing at a rate of −0.50 dB/year is shown in Figure 3. A total of 10,000 sequences were generated for each method and each true MD rate of change, and the time to detect visual field progression with 80 or 90% power and power to detect progression after 2 and 5 years were calculated.

### Statistical Analysis

To understand the relationship between the 10-2 and C24-2 MD values at cross-section and their rates of change over time, these values were evaluated in the clinical cohort. Wilcoxon signed-rank tests were performed to compare the difference in the median 10-2 and C24-2 MD values, and coefficients of determination ($R^2$) were calculated from ordinary least squares regression analysis of the relationship between these two parameters. Linear mixed models were used to evaluate the difference in the rate of 10-2 and C24-2 MD change over time, including random intercepts and random slopes to account for the participant- and eye-specific deviations from the population average change. All statistical analyses and computer simulations were performed using Stata Version 14 (StataCorp LP, College Station, TX).

## RESULTS:

### Participant Characteristics

A total of 300 glaucoma eyes from 180 participants were included and mean ± standard deviation (SD) age of the participants at baseline was 69 ± 11 years (range, 33 to 93 years), and they were followed-up for 1.9 ± 0.7 years (range, 1 to 3 years) over 4.3 ± 1.6 visits (range, 3 to 10 visits). There was a relatively similar proportion of female and male participants (55% and 45% respectively) and a similar proportion of those of African and European descent (44% and 66% respectively). The median (interquartile range [IQR]) baseline 24-2 MD and PSD of these eyes were −1.39 dB (IQR = −4.71 to 0.25 dB) and 2.25 dB (1.65 to 5.34 dB) respectively.

The median 10-2 and C24-2 MD for the eyes at baseline was −1.12 dB (IQR = −4.22 to 0.33 dB) and −0.83 dB (IQR = −4.08 to 0.44 dB) respectively, and they were not significantly different ($P = 0.187$). There was a strong, significant relationship between the 10-2 and C24-2 MD values ($R^2 = 0.92$ and 0.94 for the right and left eyes respectively; $P < 0.001$), and Figure 4 illustrates the relationship between these two parameters. Linear mixed model analysis revealed that the average MD rate of change was −0.28 and −0.30 dB/year for both the 10-2 and C24-2 respectively ($P = 0.780$). These findings demonstrate how the MD values of these two parameters are closely related both at baseline and longitudinally, and therefore the simulations were subsequently performed whilst assuming the same baseline MD and its rate of change for both methods.

### Time to Detect Central Visual Field Progression

The time required to detect central visual field progression with the 10-2 and C24-2 in eyes simulated to have an early, but clinically important degree of central visual field loss and simulated with various true rates of MD change over time are shown in Table 1 and demonstrated that the 10-2 generally detected progression earlier. For example, eyes with a true central MD rate of change of −0.50 dB/year were detected as having progressed with 90% power after 5.0 and 5.5 years of semi-annual testing using the 10-2 and C24-2, respectively; or after 3.4 and 3.7 years, respectively, if the rate of change was −1.00 dB/year. Overall, the 10-2 reduced the time required to detect central visual field progression with 80% and 90% power by between 0.3 to 0.6 years (or 79%), or reduced the total amount of central visual field lost by 0.1-0.3 dB, depending on the true rate of MD change.

## DISCUSSION

This study showed that global trend-based analysis with the 10-2 MD values detected central visual field progression sooner than C24-2 MD values in eyes with early central visual field abnormalities, when the specificities of the two methods were matched. However, the reduction in the time to detect progression with the 10-2 test was only between 7-9%, reducing the time to detect an eye with a −1 dB/year rate of central MD change by only about 0.3 years with the 10-2 compared to the C24-2, for instance. Future studies are needed to determine whether other methods for detecting progression could further exploit the increased sampling density provided by the 10-2 visual field test, or by a testing strategy that includes additional central test locations to the 24-2 visual field. Nonetheless, these findings provide evidence-based guidance for clinicians to better understanding the value-add of 10-2 visual field testing.

The finding of a very strong association between the 10-2 and C24-2 MD values observed at baseline in this study is in agreement with previous observations that abnormalities on the two tests are closely associated.[15,16] The very strong level of association observed between the MD values of these two measures is not surprising given that the same spatial locations were sampled, with the only difference being the sampling density. This also supports previous suggestions that the 10-2 MD could be estimated from the central test locations of the 24-2 tests when seeking to evaluate central visual field progression.[17] We also observed that in agreement with a previous study,[7] the 10-2 and C24-2 rate of MD change was not significantly different.

Our observation that 10-2 testing only marginally improves the detection of central visual field progression compared to the C24-2 is in disagreement with a previous study,[7] which reported a six-fold increase in the percentage of progressing eyes detected using the 10-2 and C24-2 using a PLR analysis (48% and 8% of glaucoma eyes respectively). However, the PLR analysis merely required a single location to exhibit a statistically significant negative slope less than −1dB/year, and the probability of meeting this criterion becomes inflated by virtue of the multiple testing with the nearly six-fold increase in sampling density of the 10-2 compared to the C24-2. Therefore, the increased sensitivity of detecting central visual field progression would likely have been achieved at the expense of a higher false-positive rate, the magnitude of which was not reported. This is vital to note because clinical management decisions – such as the initiation or intensification of treatment, or even the mere diagnosis of glaucoma – made on the basis of a false detection of visual field progression can have negative consequences on the individual.[18,19] Instead, we observed that the time to detect progression was only reduced by 7-9% using the 10-2 compared to the C24-2 MD values when the specificities of the two methods were matched. This was equivalent to reducing the total amount of central visual field lost by 0.1-0.3 dB. This suggests that the advantages conferred by 10-2 testing were substantially lower than previously suggested, when using the summary measure MD.

The ability to detect visual field progression is dependent on the extent of measurement variability, duration of follow-up and number of tests performed. Given that the 10-2 and C24-2 MD values are very strongly correlated, and given that our analyses controlled for the

follow-up duration and test frequency, the improved ability to detect central visual field progression with global trend-based analysis is most likely attributed to the reduction in measurement variability with the 10-2 test. Indeed, the standard deviation of the all the residuals (an estimate of variability, obtained using the linear regression analysis of the longitudinal measurements) of the 10-2 and C24-2 MD used in the simulations were ± 0.7 and ± 0.9 dB respectively (data not shown). These findings demonstrate how an almost six-fold increase in sampling density with the 10-2 test does not necessarily result in a dramatic improvement in ability to detect progression with global trend-based analysis. However, it is possible that the potential of 10-2 visual fields for the improved detection of progressive central visual field loss is not fully realized with global trend-based analysis of MD values. Future studies are needed to determine whether the increased sampling density of the 10-2 visual field test could be further exploited, perhaps through using analytical methods that account for spatial correlations,[20-22] machine learning methods[23-25] or by expert qualitative evaluation of the results.

The findings of a similar ability to detect central visual field progression with the 10-2 and 24-2 tests using global trend-based analyses of MD confer important implications for the detection of progressive central visual field loss in the clinical management of glaucoma. First, it suggests that the routine addition of 10-2 tests may not lead to detection of progression much earlier than if those additional tests were simply 24-2 tests instead. The marginal improvement in the ability to detect central visual field progression earlier with the 10-2 tests would be achieved at the expense of reducing the power to detect progressive changes occurring outside the central region. This issue becomes particularly important if clinicians choose to substitute 24-2 tests with 10-2 tests (e.g. choosing to alternate 24-2 and 10-2 tests at annual intervals, rather than performing 24-2 tests at semi-annual intervals), as it would result in a delay in the ability to detect such progressive changes. For instance, an eye with a −2 dB/year change in 24-2 MD would experience a delay in nearly 1 year for the detection of progressive visual field loss if the 24-2 testing frequency was reduced from twice to once a year.[12] However, even such marginal improvements may be warranted in certain cases given that the significance of the central visual field region for daily functioning[3-5] and addition of 10-2 tests (rather than substitution) may be a better compromise, but this should be considered on an individual-basis. Nonetheless, it is possible that the routine addition of 10-2 tests could be made more feasible by the use of a faster thresholding algorithm.[26] Furthermore, 10-2 visual field tests should still be preferred in eyes with advanced glaucoma with scotomatous non-central regions since there would be no benefit with using 24-2 visual fields to sample those locations that have already reached the measurement floor.

A limitation when interpreting the results of this study include the assumption of linearity for the rate of central visual field loss, especially when glaucomatous visual field progression could occur in a non-linear or episodic manner at the point-wise level over a long duration of follow-up.[27] However, this is unlikely to be problematic because of our use of the global measure of MD, and since both the longitudinal cohort evaluated and computer simulations were primarily performed within a short timeframe (under 5 years), where the assumption of linearity for MD is likely to be sufficient. Furthermore, we did not model pointwise visual field sensitivity values in this study (as we had done in a previous study[28])

since more visual field data would be needed to develop a sufficiently robust model of pointwise sensitivities. However, we have also recently demonstrated that point-wise event-based analyses of the visual field data performs similarly to global trend-based analyses,[29] and given that the latter analysis was performed for both the 10-2 and C24-2 study, it is unlikely that the conclusions reached in this study would differ significantly if point-wise visual field progression analyses were performed. Another limitation when interpreting the results of this study were the cut-offs used for the visual field reliability indices, since more recent evidence has emerged regarding their impact on variability of visual field MD.[30] However, given that the criteria used in this study is more conservative in general than the ones proposed recently and given that they were applied to both the 10-2 and 24-2 visual field tests, the criteria used would unlikely have a significant impact on the conclusions of this study. Finally, another important limitation in this study was the use of a population-average approach was taken for the estimation of longitudinal visual field variability, meaning that participants could have contributed data from one or both eyes and contributed different number of observations depending on the number of visits available (and the correlations between these estimates of variability were not accounted for). This approach was taken since a much larger sample size would be required to model visual field variability at the individual level (being the more ideal approach), but we do not believe this would affect the conclusions reached in this study since this approach was applied to both the 10-2 and C24-2 MD values.

In conclusion, this study showed that 10-2 tests improved the ability to detect central visual field progression compared to the central test locations of the 24-2 tests when using global trend-based analysis of MD, although it only achieved a 7-9% reduction in the time required to detect progression (or a total reduction of 0.1-0.3 dB lost). Future studies are required to determine whether other methods of visual field analysis could further exploit the increased sampling density provided by the 10-2 visual field test, and especially whether these potential advantages outweigh the loss of opportunity with characterizing visual field changes in the non-central regions. These findings provide clinicians with important evidence-based guidance on the potential value-add of MD trend-based assessment of central 10-2 visual field testing in the clinical management of glaucoma patients.

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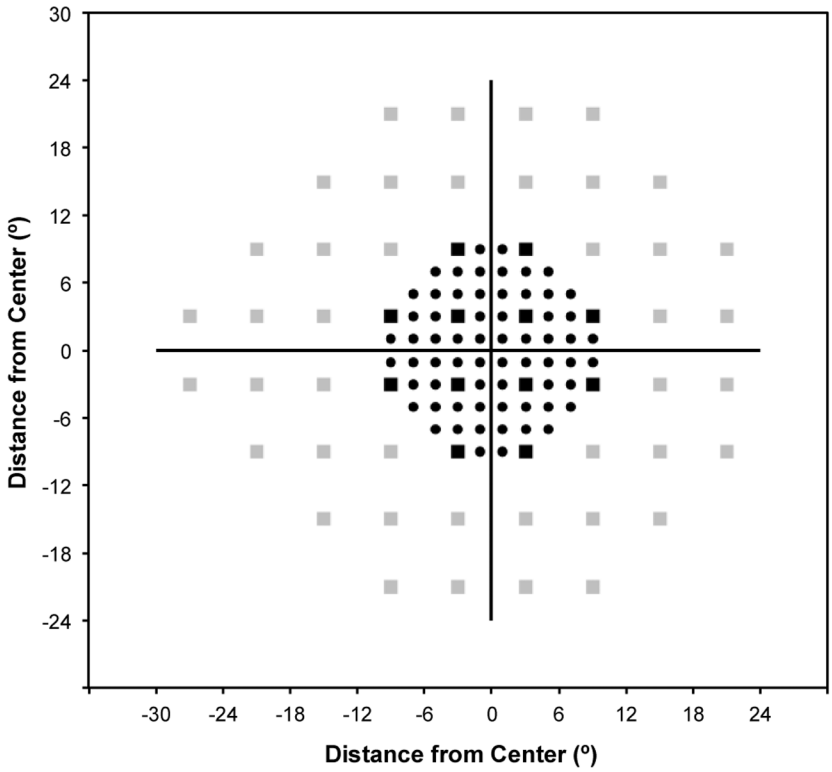


**Figure 1:**
Plot of the 10-2 and 24-2 visual field test locations (indicated by circular and square markers respectively) for a right eye, with the central 12 locations of the 24-2 test highlighted using black square markers.

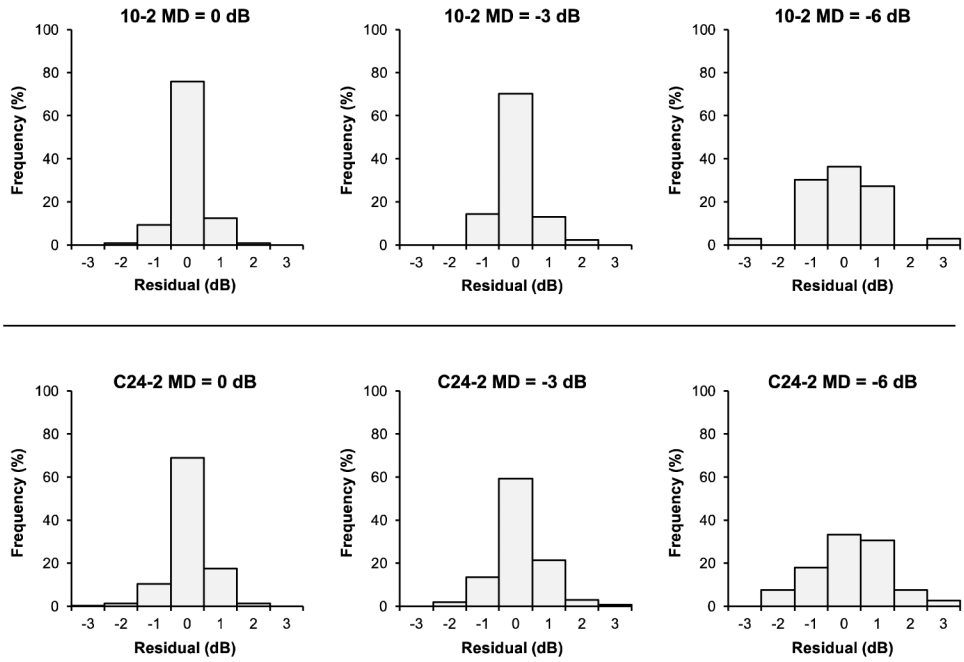


**Figure 2:**

Distribution of the residuals of the visual field mean deviation (MD) of the 10-2 test and central 12 locations of the 24-2 test (or C24-2) at three representative MD values, based on linear regression analysis of each eye in the longitudinal glaucoma cohort.

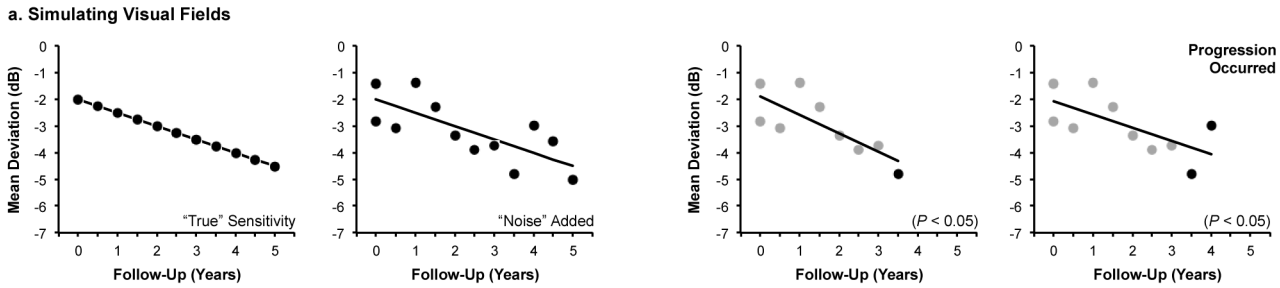


**Figure 3:**

Illustration of the process for simulating "real-world" visual field results and defining progression, shown using an example of an eye progressing at −0.5 dB/year. (**a**) Visual field mean deviation (MD) values were simulated by firstly specifying the "true" MD at each visit (left), and then adding measurement variability (or "noise") to each value (right). (**b**) Visual field progression was defined when a statistically significant negative slope was present on two consecutive visits.

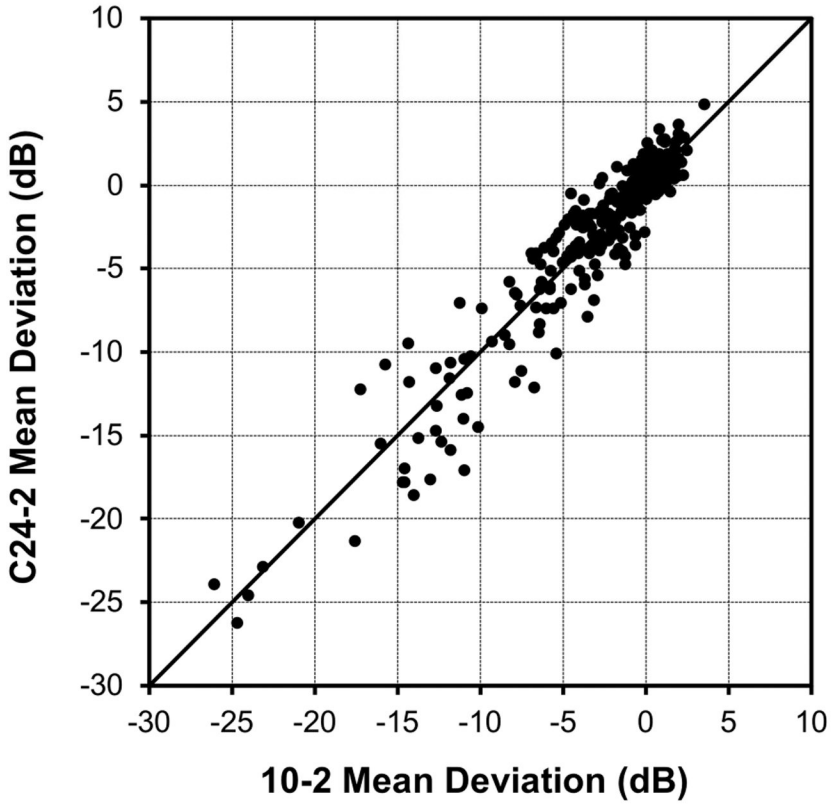


**Figure 4:**

Scatterplot of the mean deviation (MD) of the central twelve locations of the 24-2 visual field test (C24-2) against the MD of the 10-2 visual field test, with the black line representing the line of equality between these two measures.

**Table 1:**

Time and power to detect central visual field progression for different true rates of mean deviation change over time.

| | Time to Detect (years) | | Power (%) to Detect | |
|---|---|---|---|---|
| | 80% Power | 90% Power | 2 Years | 5 Years |
| **−0.25 dB/year** | | | | |
| 10-2 | 6.8 | 7.7 | 4 | 47 |
| C24-2 | 7.3 | 8.3 | 4 | 43 |
| **−0.50 dB/year** | | | | |
| 10-2 | 4.5 | 5.0 | 11 | 90 |
| C24-2 | 4.9 | 5.5 | 11 | 81 |
| **−0.75 dB/year** | | | | |
| 10-2 | 3.5 | 3.9 | 23 | 99 |
| C24-2 | 3.8 | 4.3 | 20 | 98 |
| **−1.00 dB/year** | | | | |
| 10-2 | 3.0 | 3.4 | 35 | 100 |
| C24-2 | 3.3 | 3.7 | 28 | 100 |

**SD** = standard deviation, **C24-2** = central 12 locations of the 24-2 visual field test