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Does eye examination order for standard automated perimetry matter?

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ABSTRACT.

Purpose: **In spite of faster examination procedures, visual field (VF) results are potentially influenced by fatigue. We use large-scale VF data collected from clinics to test the hypothesis that perimetric fatigue effects are greater in the eye examined second.**

Methods: **Series of six Humphrey Swedish Interactive Testing Algorithm (SITA) VFs from 6901 patients were retrospectively extracted from a VF database from four different glaucoma clinics. Mean deviation (MD) was compared between first and second tested eyes. A surrogate measure of longitudinal MD variability over time was estimated from errors using linear regression of MD against time then compared between first and second tested eye.**

Results: **Right eye VF was tested consistently first throughout in 6320 (91.6%) patients. Median (interquartile range; IQR) MD in the first tested (right) eye and second tested (left) eye was −2.57 (−6.15, −0.58) dB and −2.70 (−6.34, −0.80) dB respectively (median reduction VF sensitivity of 0.13 dB; $p < 0.001$). Median (IQR) increase in our surrogate measure of longitudinal MD variability in the second eye tested was 3% (−43%, 50%); this effect was not associated with patient age or rest time between examinations.**

Conclusion: **Statistically significant perimetric fatigue effects manifest on average in the second eye tested in routine clinics using Humphrey Field Analyzer SITA examinations. However, the average effects were very small and there was enormous variation among patients. We recommend starting with a right eye examination so that any perimetric fatigue effects, if they exist in an individual, will be as constant as possible from visit to visit.**

Key words: fatigue – glaucoma – perimetry – visual fields

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Introduction

The primary method for determining functional deterioration in glaucoma is an evaluation of visual field (VF) series over time, as measured by standard automated perimetry (SAP). Examination results from SAP are susceptible to high levels of measurement variability from different sources, including the patient themselves. Good examination procedures and instructions produce usable results in the vast majority of patients (Chauhan et al. 2008; Kutzko et al. 2000). Nevertheless, measurement variability in SAP hampers clinical interpretation of the VF. For example, several examinations need to be considered before progression or stability of the VF can be confirmed with confidence against this background of measurement variability (Chauhan et al. 2008; Crabb & Garway-Heath 2012).

Some patients exhibit increased measurement variability, or decreased VF sensitivity, on their first examinations and this is referred to as a perimetry learning effect (Gardiner et al. 2008; Heijl & Bengtsson 1996; Heijl et al. 1989). Fatigue effects, likely due to loss in concentration and attention during perimetric examination, are also likely to contribute to measurement variability and are related to the duration of examination (Henson & Emuh 2010). This fatigue effect in perimetry has been shown to be greater in the second eye tested (Hudson et al. 1994; Searle et al. 1991). Studies reporting these effects were conducted at a time before better perimetry algorithms were developed to reduce test time. More efficient examination techniques, like the Swedish Interactive Testing Algorithms (SITA Standard or SITA Fast) on the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA), have become a clinical standard and are assumed to be less susceptible to fatigue effects (Bengtsson & Heijl 1998a,b; Saunders et al. 2015).

SAP necessitates testing both eyes separately and sequentially. Conventionally, the right eye is usually tested first so that any examination order effects will be as constant as possible

from visit to visit. Few studies have considered this testing order effect in SITA testing. One study examined patients with two prior sets of SITA Standard 24-2 test results performed on the right eye first (Barkana et al. 2006). A subsequent test was performed on the left eye first. No significant differences in summary measures of the VF were found suggesting that, on average, it probably does not matter which eye is tested first. These findings might be corroborated by comparing right eye with left eye perimetry results among a large number of patients whose right eyes had been tested first. This is an idea examined in our study. If the VF sensitivity in the second tested (left) eye is worse than in the first tested (right) eye then this may suggest a testing order effect. We make the reasonable assumption that glaucoma affects both eyes similarly among a large population. This assumption is supported by results from population studies show an almost identical number of left and right eyes defined as having primary open angle glaucoma (POAG) (Chan et al. 2017; Iwase et al. 2004; Springelkamp et al. 2017). Other studies indirectly provide more evidence in favour of this symmetry, by showing similar distributions of intraocular pressure (IOP) and cup-to-disc ratios between left and right eyes (Crowston et al. 2004; Foster et al. 2000; Mason et al. 1986; Wensor et al. 1998). Measurement variability from fatigue effects in the second tested eye may also possibly accumulate over a series of follow-up visits; we explore this too.

This study investigates an eye testing order effect in retrospectively observed large-scale VF data from glaucoma clinics. First, we test the hypothesis that average VF sensitivity is worse in the second tested (left) eye compared to the first tested (right) eye in HFA SITA VFs. Second, we examine a surrogate of measurement variability in the second tested (left) eye compared to the first tested (right) eye in series of HFA SITA VFs. Furthermore, we analyse to what extent any detectable order effect is associated with patient age and the length of rest time between first and second eye examinations. As measurement variability is inherently linked to the number of VFs required to estimate the likelihood of progression, these findings could help determine if detection is being delayed due to a second eye fatigue effect.

Materials and Methods

As described elsewhere, Medisoft VF databases (Medisoft Ltd., Leeds, UK) containing 473 252 VFs from 88 954 patients were extracted in 2012 from glaucoma clinics at Moorfields Eye Hospital in London; Cheltenham General Hospital Gloucestershire Eye Unit; Queen Alexandra Hospital in Portsmouth and the Calderdale and Huddersfield NHS Foundation Trust (Boodhna & Crabb 2015; Boodhna et al. 2015; Saunders et al. 2014). Data access was granted by the Caldicott Guardians (person responsible for protecting the confidentiality of peoples healthcare information in hospitals in England) at each centre. All patient data was anonymised and transferred to a single secure database. No other clinical data was made available apart from each patient's age. Subsequent analyses of the data were approved by a research ethics committee of City, University of London and this study adhered to the Declaration of Helsinki.

Patients aged 30 years or older with VFs from the HFA using Goldmann size III (white-on-white) stimuli with the 24-2 test pattern acquired with either SITA Standard or SITA Fast testing algorithms were included in the study. Patients were only included if they had at least six recorded VF examinations (consistently with SITA Fast or consistently with SITA Standard) where both eyes were tested on the same day. We did not exclude patients with longer follow-ups but for our analyses we only considered the first six examinations. The first VF in each series was then omitted in order to attempt to account for perimetric learning effects (Gardiner et al. 2008; Wild et al. 1991). This left a total of 6901 patients for analysis. These data represent a population of people receiving routine follow-up in glaucoma clinics in England.

For our analyses, we only included patients where eyes were tested in the same order at each examination, with right eye tested first. The first VF examination of each series was defined as the baseline VF. HFA mean deviation (MD) values were extracted for each VF for each eye. MD estimates overall VF sensitivity, relative to healthy age-matched observers, with more negative values indicating greater VF sensitivity reduction. Average MD for first eye tested (right) and second eye (left) tested, from the baseline examinations only, were compared; no difference in these values would suggest no average systematic eye testing order effect.

To investigate differences in long-term measurement variability in the eye tested first or second we considered the MD over the five examinations for each patient. Ordinary least-squares linear regression of MD against time was used to extract errors (predicted values minus the observed sensitivity [dB] values) at each examination (Fig. 1). The mean of these absolute errors (MAE) was used as our estimate of long-term measurement variability. For example, a series exhibiting high measurement variability would have variable MD values (after removing any trend for change over time) yielding a high MAE value. The increase (or decrease) in MAE for the second tested eye compared to the first tested eye, relative to the average MAE in both eyes, was calculated; this effect, expressed as a percentage, was our surrogate for long-term measurement variability due to an eye testing order effect (See Fig. 1). VF measurement variability is directly related to the amount of VF loss (Russell et al. 2013). For example, a patient with early VF loss in their first tested eye but advanced loss in their second tested eye will likely have more measurement variability in the latter regardless of any fatigue effects. Therefore, in order to minimise noise in our estimates we also repeated our analyses on a subset of patients where overall VF loss was similar in both eyes (left and right eye baseline MD within 3 dB of each other).

Furthermore, we examined if the eye order effect, if present, was associated with the age of a patient and the rest time between the first and second eye exam. All analyses were done using R (R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, URL: http://www.R-project.org, 2008).

Results

Median (interquartile range [IQR]) age of the patients and length of follow-up

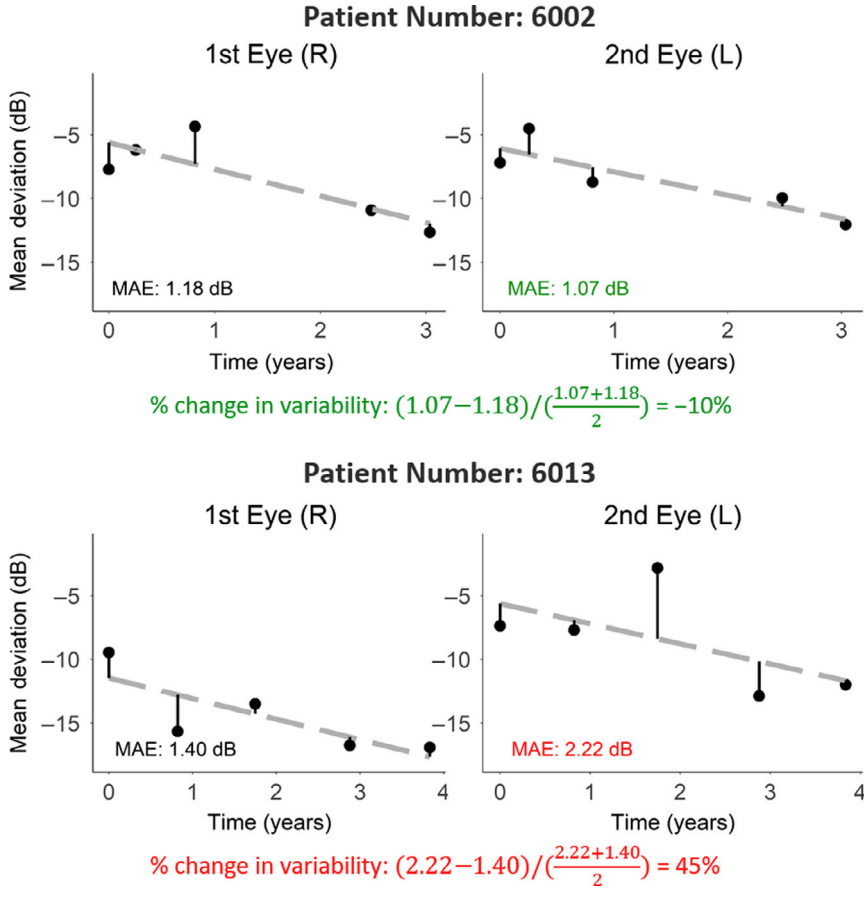

Fig. 1. Calculation of absolute errors (vertical lines) and relative MAE increase (%) for two different patients. Patient 6013 has more long-term measurement variability in the second eye tested with a 45% increase in our surrogate measure. In patient 6002, the long-term variability is more similar in both eyes.

for the five examinations was 66 (56, 73) and 4.5 (3.5, 5.8) years respectively. From the population of 6901 patients with sufficient VF follow-up, 6320 (91.6%) had consistently been examined in a right eye then left eye sequence at each SAP examination. Only seven (0.1%) patients had been consistently examined in left then right eye sequence. The remaining patients (574; 8.3%) were excluded due to the eye testing order not being consistent (not always right eye first). These numbers illustrate the remarkable adherence to the convention of testing the right eye first in perimetric examination in the clinic.

Median (IQR) MD in the first tested (right) eye and second tested (left) eye was −2.57 (−6.15, −0.58) dB and −2.70 (−6.34, −0.80) dB respectively. This average decrease in MD from first to second tested eye was statistically significant (Wilcoxon signed rank test; $p < 0.001$) but small in magnitude (median difference of 0.13 dB, 95% CI: −0.26, −0.02). This average worsening in VF sensitivity in the second eye tested could be explained by a fatigue effect but the magnitude of the average effect is small.

Measurement variability in MD values from series of VFs performed in clinics, as measured by our MAE value, varies considerably between eyes in the same patient (Fig. 2). Median (IQR) increase in second tested (left) eye measurement variability (order effect) was 3% (−43%, 50%) and this was statistically significant ($p < 0.001$). This effect was small and obviously not consistent across all patients. Yet, it does indicate that on average the second tested eye in SAP accumulates slightly more measurement variability during a follow-up in a routine clinic. This average effect remained unchanged (median = 3%) when we restricted analysis to patients with similar overall VF loss in both eyes ($n = 4528$). Yet, as would be expected, the IQR narrowed, but only moderately (−39%, 48%). We also repeated the analysis on a sub-sample of the patients that had series of 10 VFs ($n = 745$ patients) and as would be expected, the IQR narrowed again to −30% to 33%. The eye testing order measurement variability effect was not associated with the age of a patient ($p = 0.20$), nor was it associated with the time (seconds) between testing the first and second eye ($p = 0.53$) with $R^2 \sim 0$ in both cases (Fig. 3). So, any accumulative measurement variability in the second tested eye is not inflated in older patients or associated with the period between each eye examination.

Discussion

Our results indicate average VF sensitivity, as estimated by HFA MD, was slightly worse in the second eye examined (left eye) in a large sample of over 6000 people. Assuming no physiological reason for left-right eye VF sensitivity differences we suggest this sensitivity decline might be attributed to a fatigue effect. We also explored the accumulation of measurement variability in the second eye tested using a novel serial analysis of MD variability. Results from this analysis suggest some evidence of more measurement variability in the second eye tested. It is important to note this order effect is an 'average' effect and likely too small (3% increase) to impact on results from routine clinics. For example, it has been suggested that a decrease in longitudinal variability of about 20% is needed to detect a progression one visit earlier using linear regression of sensitivity values over time (Turpin & McKendrick 2011). Still, in situations where small differences in average precision could affect the statistical power to detect an outcome measure, such as in a group of participants in a clinical trial, it might be worthwhile to test the 'study eye' first.

Several factors contribute to measurement variability in automated perimetry. For some patients this perimetric variability may be inflated by examination fatigue, which will worsen during prolonged testing. Therefore, the second eye examined may be more susceptible to fatigue induced variability. This leads to at least two scenarios in the clinic: an instruction to examine the eye of interest first or examining eyes in a consistent order so that any

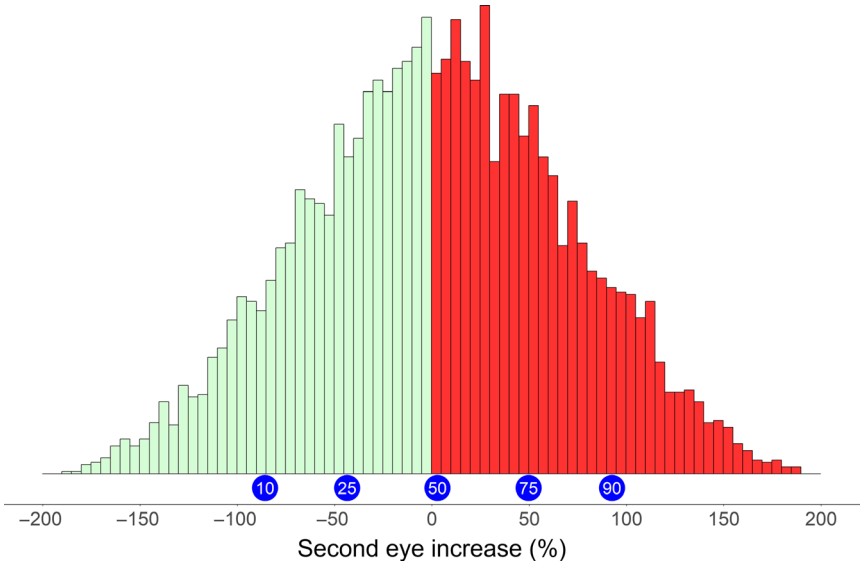

Fig. 2. Distribution of the percentage change in second eye variability with labelled median and 10th, 25th, 75th and 90th percentiles.

fatigue effects will be as constant as possible from visit to visit. More simply, the right eye is always tested first following a convention for most eye examinations; this was supported by the results from our study with over 90% of patients consistently being tested right eye first.

Most studies highlighting perimetric fatigue were done when automated perimetry was hampered by longer exam times (Hudson et al. 1994; Johnson et al. 1988; Searle et al. 1991). SITA strategies halved testing times compared to the full threshold algorithms and have become the standard for HFA examinations (Bengtsson & Heijl 1998a,b; Bengtsson et al. 1997; Wild et al. 1999). One study, with a similar aim to ours, recruited patients from clinics with two prior sets of SITA Standard 24-2 test results performed on the right eye first and then deliberately examined them once with the left eye first. There was no statistically significant difference in the MD, or the test reliability measures, among the three test results for either eye. In contrast, we did find a statistically significant difference in MD in our study. It is, however, important to reiterate that the average sensitivity decline between first and second eye tested is very small and we conclude it probably still does not matter which eye is tested first when considering MD. A series of factors thought to influence SITA HFA VF measurement variability, or spurious changes in VF sensitivity, were thoroughly investigated by Montolio et al. (2012). Not-so-obvious factors such as *the time of day* and *the season* (time of year) when examinations are performed were considered. The effects were real and statistically significant. However, all of these effects are rather small in magnitude. Similarly, the eye examination order effect on longitudinal variability that we observed in our study is relatively small. We conclude that fatigue in the second eye tested does slightly increase measurement variability in that eye during follow-up but is similar in magnitude to the effects generated by other minor factors described in the literature (Bengtsson & Heijl 2000; Bryan et al. 2015; Gardiner et al. 2009; Montolio et al. 2012). In other words, the average effect is small given the overall variability. Optimising the frequency of VF testing, or only making clinical decisions after a sufficient number of VF examinations have been administered, is likely the best way to counteract the effects of this measurement variability (Boodhna & Crabb 2016; Chauhan et al. 2008; Crabb & Garway-Heath 2012; Jansonius 2010). Ultimately, to minimise VF variability, patients

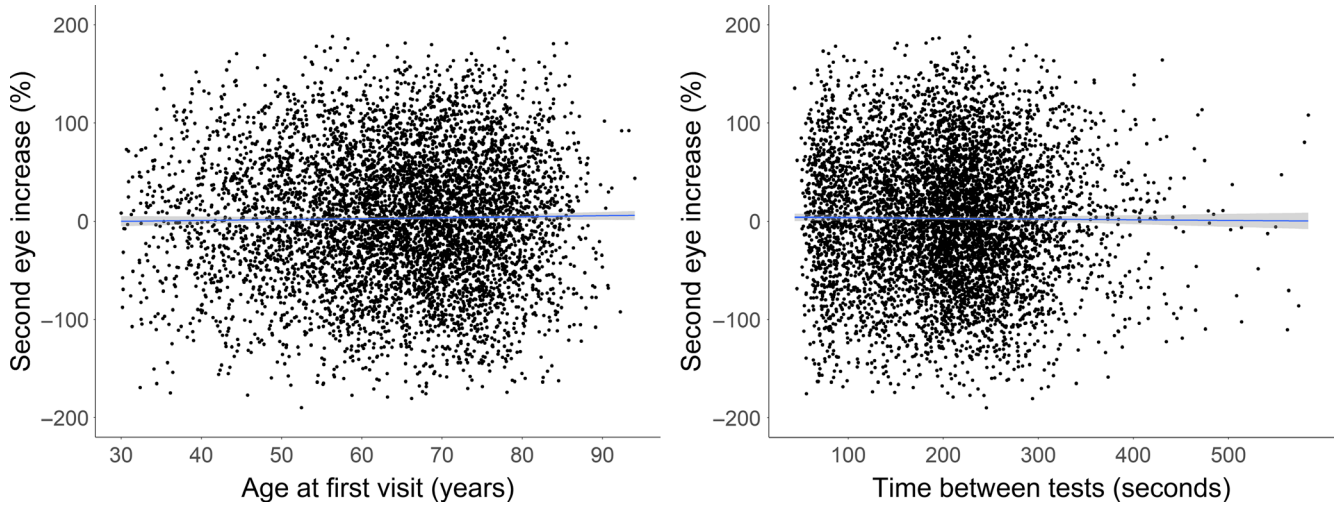

Fig. 3. Scatter plots showing the change in variability as a function of baseline age (left) and rest time between exams (right) with fitted linear model (blue). The blue line would slope upwards (or downwards) to indicate a change in effect size with age or rest time. The time between tests is censored at 600 seconds resulting in 0.3% of patients being excluded.

should be encouraged to produce reliable results by making sure they understand what to expect, and what they need to do during an examination, even if they have done them several times before (Chauhan et al. 2008; Glen et al. 2014; Kutzko et al. 2000).

We found no association between change in between eye measurement variability (order effect) against age of patient, or against the rest period between right and left eye examination. These results indicate that older age or a shorter rest period between examinations did not explain any of the increase in between eye variability. Whilst the latter is interesting, interpretability is very limited by the retrospective nature of our data. For example, decisions about how long to 'rest' patients between examinations may be made because the patient is already tiring, complaining or asking for a rest.

In contrast to SAP, Frequency Doubling Technology (FDT), incorporated in the Humphrey Matrix perimeter (Carl Zeiss Meditec), employs an examination stimulus that uses a low spatial frequency sinusoidal grating that undergoes high temporal frequency counterphase flicker. The second eye tested in FDT perimetry has been shown to have significantly higher thresholds (reduced sensitivity) when compared to the first (Anderson & Johnson 2002; Anderson & McKendrick 2007); a much larger eye examination order effect than that seen in SAP. These studies concluded the eye testing order effects in FDT perimetry were less likely to be wholly related to fatigue. Instead, the investigators in these studies postulated that the differences were more likely due to light adaptation state between eyes occurring with the use of opaque monocular patching and the effect could be largely abolished by using a translucent patch.

Our study was multi-centre and utilised a 'big data' approach to the analysis by incorporating anonymised data from several thousands of patients. Using a large repository of electronically stored VF data is useful for auditing different aspects of glaucoma related healthcare such as testing hypotheses about the management of patients. Moreover, these data represent unselected people in glaucoma clinics that are receiving routine care and therefore estimates are directly meaningful to 'real-world' practice.

Our study has some key limitations. The study only considers data retrospectively. We had no control over the data used for assessing change in long-term variability; for example, some patients might have deliberately not been followed with VFs in these clinics because they fatigued so badly during the testing. These people would not be represented in our study. HFA reliability indices (estimates for false positives, false negatives and fixation loss) were not used in this study because most were missing from the original database and it was not possible to extract them from the electronic patient record. This is a very important limitation because HFA reliability indices are sometimes used to exclude poorly carried out examinations in clinical practice. These reliability indices themselves can be unreliable however (Bengtsson 2000; Bengtsson & Heijl 2000; Chauhan et al. 2008). Nonetheless, analysis of these metrics in first and second eye tested would have been useful to assess potential fatigue between examinations and might be the subject of another study. Finally, whilst our sample of data was large and representative of people (>30 years) in glaucoma clinics in England, our findings might not hold for when SAP is used in children or in very old individuals.

The order effect we detected is an average effect and it varies enormously between patients. A suggestion for future work would be to design a study that can help determine how well a particular patient can remain vigilant and avoid fatigue. We certainly need better ways of determining which individuals are more likely to produce reliable perimetric results so we can better use perimetry resources (Boodhna & Crabb 2016). Better use of eye tracking to measure surrogates of vigilance, like pupil diameter, might better estimate fatigue during perimetry (Henson & Emuh 2010). Moreover, occlusion of one eye while testing the first could also affect variability in the second tested eye in perimetry in some people. This might be the result of perceptual deprivation (ganzfeld) effects whilst the eye is occluded (Fuhr et al. 1990). Furthermore, the background adaptation for an occluded eye in perimetric testing will be lower than that of the tested eye even with the use of a translucent eye patch (Anderson & Johnson 2002; Anderson & McKendrick 2007; Bierings et al. 2018; Dul et al. 2015). It would need a prospective study to examine these effects in SAP and this could be the subject of future work.

In conclusion, we observed statistically significant average perimetric fatigue effects in the second eye tested in routine clinics using HFA SITA examinations. However, the effects were very small and there was enormous variation meaning some patients may experience a perimetric fatigue effect by the time their second eye is examined, whilst others are unaffected. Clinically it therefore seems reasonable to continue to start with a right eye examination so that any perimetric fatigue effects, if they exists in an individual, will be as constant as possible from visit to visit. Perhaps, in situations where measurement precision needs to be maximised, such as in a clinical trial using VF measures as an outcome or endpoint, it may be worthwhile to examine a 'study eye' first.

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