# An Investigation into the Effect of Increasing Target Size for Visual Sensitivity Measurement in Normals and in Early Glaucoma

by

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## AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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# Abstract

The clinical standard method of measurement for clinical visual sensitivity is currently Standard Automated Perimetry with a size III target (SAP III). However, there are many factors that can make the results unreliable. While there is literature that confirms the benefit of increasing target size for measurement of visual sensitivity in the later stages of glaucoma, there is little literature that looks into the effect of increasing target size for the measurement of visual sensitivity in early glaucoma. Furthermore, the effect of increasing target size for the measurement of visual sensitivity in normals is largely undefined. We performed 2 studies to determine the effect of increasing target size for the perimetric measurement of both normals and in participants with very early glaucoma.

In the first study (chapter 2), 40 normal participants (one study eye) performed 3 full threshold visual fields at 2 separate visits, no more than 90 days apart. The target sizes used were size III (0.43° diameter), size V (1.72° diameter) and size VI (3.44° diameter). We investigated the interaction of the different target sizes by regressing the average field threshold for each participant against age in both decibels and candelas. We found an expected difference in sensitivities between the different target sizes for the decibel analysis, but an unexpected difference in thresholds between the target sizes for the candela analysis. Possible reasons for this unexpected difference in total light energy are discussed.

In the second study (chapter 3) we investigated the effect of increasing target size in 17 participants with very early glaucoma (perimetric mean deviation of equal to, or better than, -4.0dB). Each participant underwent 3 full threshold visual field tests, using 3 different target sizes, at 2 separate visits (no more than 90 days apart). We computed empirical probability plots for each participant and target size: Size III (0.43° diameter), size V (1.72° diameter) and size VI (3.44° diameter), where normal percentile limits were based on the first study - chapter 2. We then compared the number of normal and abnormal test locations at each defect depth (5%, 2%, 1% and 0.5%) between SITA-Std and the 3 different target sizes (full threshold) using a repeated measures ANOVA. We found there to be no statistical difference in the number of abnormal locations detected between SITA-Std and the 3 target sizes. However, when analysing the empirical probability plots there was an apparent clinical difference between the locations of abnormality detected between SITA-Std and the larger size VI target, with the size VI giving less consistent defect locations.

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# Chapter 1: Literature Review

## 1.1 Glaucoma

Glaucoma, the world's second most prevalent cause of blindness[1], is an umbrella term for a range of progressive ocular diseases. The definition of the glaucomas has changed over the years, with a current definition being that it is a range of diseases that arise as a result of various risk factors, including increased intraocular pressure (IOP), with a common consequence of optic neuropathy and ultimately, loss of visual sensitivity[2]. The types of glaucoma are many, but almost all occur in the older generations and can include primary open angle glaucoma, secondary open angle glaucoma, including pigmentary glaucoma and pseudoexfoliation glaucoma, and primary or secondary closed angle glaucoma. Due to the high prevalence of the glaucomas and the severe visual consequences, it is important that progression of this disease can be monitored accurately, so that treatment can be administered and adjusted effectively.

## 1.2 Structure and Function

In the literature, the evidence for a structure-function relationship when measuring defect in glaucoma is much debated. Harwerth et al.[3] investigated the correlation between structural and functional measurements of retinal ganglion cells (RGCs) and their axons in adult rhesus monkeys, both for the normal population and monkeys that were laser treated to scar their trabecular meshwork and induce high IOP (experimental glaucoma). When the functional Standard Automated Perimetry (SAP) measurements and the structural Optical Coherence Tomography (OCT) measurements were converted to a shared parameter of RGC populations, the measurements were correlated for both the controls and the experimental glaucoma populations. They suggested that, to accurately gauge the correlation between retinal function and structure measurements, there should be a common denominator, such as RGC population, to compare the 2 methods of neural loss. Furthermore, they proposed that the discrepancy between function and structure measurements in other studies could be due to the lack of sensitivity of many of the instruments that measure either parameter: It is thought that OCT is much more sensitive to detecting the small, early RGC changes, whereas SAP is more apt for detecting gross defects in advanced glaucoma due to its large clinically useful range (dynamic range)[3]. In 2010, Harwerth et al.[4] further explored these concepts and proposed a model that could

estimate with reasonable precision the neural loss from both visual sensitivity measurements and retinal nerve fibre layer (RNFL) thickness in patients with glaucoma using time domain OCT and SAP. However, the authors did state that the relationship should be reconsidered using newer technology to measure the RNFL thickness, such as a spectral domain OCT (SD-OCT), to increase the accuracy and precision of the model.

More recently, another study[5] showed that there is a weak linear relationship between structural and functional damage, even in suspect/early glaucoma, when comparing visual sensitivity measured by SAP and rim area (RA) measured by Cirrus high definition spectral domain optical coherence technology (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA). Optic disc RA measurement appeared to have a stronger correlation to SAP measurements than RNFL thickness in this study. To second the study by Nilforushan et al., Leite et al.[6] used very similar instruments (Cirrus SD-OCT and SAP) to show that there was a linear correlation with a weak –moderate strength of relationship ($r^2$ = 0.203) between structural and functional damage in early/suspected glaucoma patients when perimetric sensitivity was converted to a linear scale. The authors suggested that, had they also included patients with advanced glaucoma, the results may have shown a much stronger correlation. This comment was based on the results of a relatively recent study which found a stronger structure/ function correlation when including a proportion of more advanced glaucoma participants[7].

There have, however, been studies to suggest that structural damage in glaucoma precedes functional damage[8-10]. Sommer et al.[8] suggested that 60% of glaucomatous eyes showed RNFL damage before visual field loss. However, these results are difficult to compare with previous studies as their results relied upon 2 examiners measuring both the functional and structural loss with a Goldmann perimeter and a Zeiss fundus camera respectively. In essence, this study relied heavily on the experience of the examiners. A later study by Matsumoto et al.[9]showed, by a more objective method, that RNFL thickness was already decreased in participants with glaucoma before visual sensitivity became reduced when using the Humphrey Field Analyzer (HFA) and an updated version of the Nerve Fiber Analyzer (NFA, GDx Version 1.012) to measure visual field loss and RNFL thickness respectively. However, this study only measured patients with primary open angle glaucoma (POAG) and normal tension glaucoma (NTG), so did not encompass the full range of the glaucomas. Interestingly, another recent study evidenced that not all types of optic disc damage resulting from glaucoma exhibit the same rate of structural or functional progression[11]. This study showed that patients with focal optic disc damage have a more rapid decline in visual field loss and optic disc change than other types of optic disc damage, such as diffuse or sclerotic optic disc damage. However,

despite a more rapid structural and functional loss in focal disc damage, only the functional loss was shown to be statistically significant[11]. The results of this study highlight that all types of glaucoma should be included in the study sample to gain a non-biased result across the range of glaucomas. The lack of structure-function correlation found in a proportion of the literature could also be due to the lack of a common denominator when comparing the variables, as proposed by Harwerth et al.[3].

However, despite the discrepancy in the literature, there are studies which present evidence that functional damage is correlated with structural glaucomatous damage[4, 5, 7], although the conclusions that are drawn depend on the precision and accuracy of the instruments used to measure both structural and functional damage and a common denominator to link the two variables being measured [3]. In short, although there is still debate as to the exact relationship, functional damage is known to be correlated with structural damage in glaucoma. For this reason, it is important that functional progression is monitored accurately at all stages of the disease.

## 1.3 Measuring Functional Loss in Glaucoma

Visual sensitivity, measured by a perimeter, has been, and still is, the clinical standard for evaluating functional progression of the disease. More specifically, Standard Automated Perimetry with a white Goldmann size III target (SAP III) presented on a white background is the current clinical standard when measuring functional defects in glaucoma. SAP III has been shown to be a compromise between blur [12], accuracy of result [13] obtained and effective dynamic range (EDR)[14]. An early study[13] showed that smaller targets measure absolute scotomas more accurately. In this study the blindspot, used as an absolute scotoma, was measured with Goldmann stimuli I through V. They demonstrated that larger targets measured the blindspot as more relative and less defined than smaller targets and attributed this to the increasing light scatter with the larger targets. They suggested that, as a greater amount of light (i.e. larger stimulus) passed through the optic media of the eye, there was increased scattering of the target, creating a larger halo of light. In normal eyes, lateral inhibition would eliminate these haloes. However, this mechanism is not active at borders of seeing/non-seeing retina (i.e. scotomas). The authors' conclusion was that, when detecting scotomas that are small in spatial area, the smallest target size possible should be used. While Anderson et al. also agreed that smaller targets gave a more accurate measurement of scotomas; they determined that larger targets were less influenced by dioptric blur in uncorrected peripheral refractive error[12]. One other advantage of using a larger target is that EDR increases with increasing target size[14]. Therefore, SAP III is a compromise between maximising

EDR, optimising accuracy of defect detection and dioptric blur effects and is currently used as the clinical standard to measure visual sensitivity in both healthy patients and in ocular pathology, such as glaucoma.

However, when measuring visual sensitivity by means of a perimeter, there has been much research into factors that can cause the results to be unreliable. More recent literature that has revisited this area of research shows that these factors include, but are not restricted to, learning effects[15, 16], fatigue[15], pupil size[17, 18], media opacities[19], foveal and peripheral dioptric blur[12], level of instruction given[20] and both short term[21] and long term fluctuation[22]. In addition, due to the limited number of stimuli presented at each location in the interests of a maintaining a test that is of reasonable length, the staircase threshold method may possibly measure inaccurate results. One other main concern is that variability with SAP III is shown to be high in areas of retinal pathology[22, 23] resulting in poor accuracy when monitoring progression of visual sensitivity in these areas[24]. An early study by Heijl et al.[23], measuring perimetric test/re-test variation in 51 patients with glaucoma using SAP III, showed that variation is a product of both defect depth and eccentricity. For participants with initial visual field loss in the range of approximately -8 to -18dB, the 95% prediction interval of re-test thresholds varied across almost the whole extent of possible sensitivities. Furthermore, with shallower defect depth, variation increased as a factor of eccentricity. In light of these results, the authors concluded that the greater the retinal damage, the larger the test/ re-test variation, although they also showed that variation in much greater abnormality reduces. Furthermore, in areas of shallow defect depth, variation is greater in the peripheral field. A recent study[22] that looked at long term fluctuation (LF) in Humphrey Field Analyser (HFA) SITA standard perimetric testing across different stages of glaucoma (classified using the GSS2 scale), confirmed this early study by Heijl et al., showing that LF increased up to stage 4 in a curvilinear fashion. Interestingly, at stage 5, they also found a decrease in LF and suggested this could be due to the scotomas presenting in more advanced glaucoma being much more absolute and less relative, showing less fluctuation. These results by Fogagnolo et al. do show that LF becomes, in general, greater as glaucoma progresses. Henson[25], using frequency of seeing curves to measure perimetric intra-test variability, also concluded that variability increases with decreasing retinal sensitivity. With these findings in mind, it is vitally important that ways are found to decrease the variability of results in these damaged retinal areas to enable an accurate prediction of disease progression within glaucoma.

## 1.4 Increasing Target Size

There have already been promising results from studies that have, in recent years, revisited the effect of target size on perimetric variability, suggesting that increasing target size in SAP decreases variability in areas of manifest retinal disease[26-28]. One study showed that, when testing 10 normal participants using an HFA perimeter with Goldmann target sizes I - V, the size IV and V stimuli resulted in a reduced short term fluctuation while the smaller targets (size I and II) had an increased short term and total fluctuation[21]. The authors did, however, state that as their study did not include any patients with glaucoma or elderly patients, further investigation would be needed to determine if these results held true for these additional groups. In 1997, Wall and colleagues began a series of investigations looking at the effect of target size on perimetric results in patients with glaucoma[14, 26-30]. Their first study in this series[26] investigated how increasing target size in automated perimetry affected perimetric variability in patients with well established POAG. They showed, using frequency of seeing curves, that the standard deviations of intra-test variability were significantly reduced for the size V target compared to size III or size I target for patients with glaucoma at abnormal test locations. This study, however, was carried out under quite artificial test conditions that did not mimic real life. Each patient was only tested in 2 test locations (controls: central and peripheral locations; glaucoma patients: normal and abnormal locations), with 205 stimulus presentations varying in stepwise threshold at each location. A more recent study by Wall et al.[28] tested 120 patients with glaucoma (encompassing a range of severities) and 60 age-matched controls with 3 different perimeters (the HFA perimeter was utilized once with a size III target and once with a size V target). This investigation showed that re-test variability with the perimeters which employed larger target sizes was lower in areas of reduced sensitivity than those that employed smaller target sizes. Matrix perimetry (target size of 4°diameter) and motion perimetry (range of target sizes between 0.1 and 8° diameter), showed no clinically meaningful increased variability in areas of decreased sensitivity, such as that of both SAP measurements. Furthermore, SAP V (with a target size of 1.72 °diameter) showed reduced variability in areas of lower sensitivity compared to SAP III (with a target size of 0.43 °diameter). A later study also promoted the use of SAP V by showing that the EDR for SAP V is about 1 log unit greater than that of SAP III[14]. There is also evidence for a similar precision of testing between the 2 target sizes when monitoring moderate glaucoma[27]. In 2013, Wall et al. continued this research, investigating the effect of a target size V over a target size III on variability of mean defect[29]. They found that there was only small decrease in variability of mean defect with size V target compared to a size III target. Nevertheless, these results serve to add to, not take-away from, the

evidence that is gathering to indicate that SAP V would be more accurate in detecting functional loss in moderate/established glaucoma, compared to SAP III[14, 26-28]. To take the research one step further, Wall et al. also looked at the performance of target size VI compared to size V and III[30]. When comparing the amount of abnormal test locations for a group of 120 glaucoma participants (encompassing all stages of the disease) between the 3 different target sizes, they found that the size V target was the most sensitive. When stratified into MD bins, the size V target was still the most sensitive for the lower MD bins, while size VI was the least sensitive. This suggests that there is a cut-off point where a further increase in stimulus size can be detrimental to the perimetric results.

There is also evidence in the literature that enhanced perimetry results with increasing target size is not confined to SAP, but has been demonstrated in other types of perimetry. Quaid and Flanagan[31] used normal participants to show that, with flicker defined form perimetry (FDF), as stimulus size increased, variability within subjects decreased and sensitivity increased at all eccentricities. In their 2009 study, Wall et al.[28] showed decreased variability, not only with SAP V compared to SAP III, but with the increased target size in matrix and motion perimetry in areas of retinal defect in participants with glaucoma. The results from the literature described here show promise that, regardless of perimetric method, increasing target size could be the key to obtaining more repeatable perimetry results, especially in retinal areas that have been subject to neuronal damage.

There is certainly evidence to suggest that a larger size V target could be beneficial in measuring retinal sensitivity more accurately across the progression of glaucoma[14, 26-29], and early evidence to suggest that increasing the target size to a size VI may be detrimental to detection of perimetric abnormality in disease[30]. However, the current literature looks at these effects across all stages of the disease, with a focus on moderate to established glaucoma. This research must be stretched further to investigate the effect of increasing target size on very early glaucoma.

## 1.5 Spatial Summation

Spatial summation is the summing of information over space. In the case of the retina, light energy over a certain area will be combined[40]. Spatial summation occurs across the retina and increases relative to the size of receptive fields with increasing eccentricity. Ricco's Law states that, within each critical area (Ricco's Area), as threshold intensity doubles, size of the target halves to maintain the quanta of energy reaching the retina[32]. As target size increases above the critical area incomplete

summation occurs, relative to Piper's Law[32]. Ricco's area is dependent on the size of receptive fields in the retina, and has been shown to enlarge with increasing retinal eccentricity for both s-cones and l-cones when each type of cone was isolated and tested for foveal and peripheral spatial summation characteristics. The authors suggested that this was due to larger receptive fields and more convergence of photoreceptors in the periphery[33] and suggested it is likely that Ricco's area is dictated by density of RGCs in each area of the retina, explaining why Ricco's area increases with increasing retinal eccentricity.

Interestingly, it has been shown that, in infants, a greater extent of visual field is measured with a 6° diameter target, compared to a 1.5° diameter target[34]. These results did not hold true for healthy adults though, and one reason for the difference was suggested to be due to infants having larger spatial summation properties in the peripheral retina compared to adults. These findings could be very relevant when measuring the visual field of participants with glaucoma, especially since spatial summation is a characteristic that has been shown to change in patients with glaucoma[35]. If differing spatial summation properties can affect the measurement of visual fields in infants[34], then the measurement of visual sensitivity in patients with glaucoma could also be adapted if there exists changes in spatial summation properties in the ocular disease.

There is also evidence in the literature to support changes in Ricco's area with age, although this literature is conflicting. The outcome of one early study showed that there was no change in spatial summation across different age groups[36]. The results of this study were limited, however, since spatial summation was only measured along the superior temporal oblique meridian in all participants. A much more recent study investigating the full extent of the human retina, shows that the density of neurones in the retina declines per year, although this effect is much more pronounced when considering the entire retina than it is in the foveal regions[37]. This conclusion is consistent with the findings of Malania et al. in 2011, who also broadened their study to look at the effect of RGC loss on spatial summation[38]. These authors showed that spatial summation increased with age in the parafoveal area, due to loss of RGCs. While they explained the significant parafoveal increase in spatial summation of the older participants by a related loss of RGCs, they justified the preserved spatial summation properties in the fovea by the minimal age-related loss of RGCs in the foveal region of the retina.

Bearing this in mind, it is also thought that there could be alterations in receptive fields and spatial summation properties as a result of the progressive loss of RGCs in glaucoma[35], although there is literature that rejects this theory[39]. Battista et al.[39] investigated how spatial summation differed

across the magnocellular (M) and parvocellular (P) pathways, and also between controls and patients with primary open angle glaucoma (POAG). Although this study did show that spatial summation characteristics differ across the M and P pathways, the elevation in threshold with differing stimulus size when measured in controls and POAG subjects was not significant. The authors did, however, acknowledge that if they had used a wider range of stimulus sizes they may have obtained a different result. Redmond et al.[35] undertook an experiment to monitor how Ricco's area and spatial summation changes within the early stages of glaucoma. By comparing healthy subjects to patients with early glaucoma, they showed that there was a significant increase in size of Riccos' area for achromatic and s-cone specific stimuli in the early glaucoma participants. They concluded that Ricco's area becomes enlarged even at the early stages of the disease and suggested this may be a result of each receptive field needing a critical number of RGC to enable the stimulus to be detected. It was also suggested by these authors, that increasing target size in relation to the enlargement of Ricco's area in patients with glaucoma would be beneficial in encompassing areas with a greater number of healthy RGCs, despite inevitable glaucomatous loss of RGC. This result, however, is confined to early glaucoma and has not yet been proven in the later stages of the disease. Further study needs to be carried out in this area to confirm these results, but these initial studies show promise that increased areas of spatial summation in early glaucoma could serve as a means of explaining the reason for more accurate perimetry results with larger stimulus sizes when measuring functional loss in glaucoma.

## 1.6 Summary and Conclusion

In conclusion, there is evidence to show that increasing target size from Goldmann size III to Goldmann size V decreases perimetric variability in both normals[21] and patients with moderate to advanced glaucoma[26, 28]. Furthermore, EDR is also greater with a size V target[14]. It is possible that decreased variability with increasing target size can be attributed to the spatial summation properties changing with progression of glaucoma[35]. Volbrecht et al.[33] suggested that spatial summation properties change with loss of RGCs to maintain a constant density of neurones within the critical area, which could explain this phenomenon.

Despite these findings, SAP III is currently used as the clinical standard to measure visual sensitivity, and there is evidence to show that use of larger target sizes reduces the detection accuracy of relative scotomas[13]. Since early functional change in glaucoma presents as relative scotomas and this research has mainly focused on patients with moderate to advanced glaucoma, there needs to be

further study at looking into whether increasing target size in early glaucoma is beneficial in decreasing variability, while also sensitive enough to detect relative scotomas.

# Chapter 2

# The Effect of Increasing Target Size on the Measurement of Visual Sensitivity in Normals: Defining Normal Limits

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## 2.1 Overview

Purpose: To investigate the effect of increasing perimetric target size for the measurement of visual sensitivity in normals.

Methods: Forty normal participants were recruited and 3 visual fields were performed on one study eye at 2 separate visits, no more than 90 days apart. The target sizes used were size III (0.43° diameter), size V (1.72° diameter) and size VI (3.44° diameter).We investigated the interaction of the different target sizes by regressing the average field threshold for each participant against age in both decibels and candelas.

Results: We found an expected difference in sensitivities between the different target sizes for the decibel analysis, but an unexpected difference in thresholds between the target sizes for the candela analysis (total light energy). When values were converted back to size III dBs, the minimum fitted threshold difference in total light energy was 4.68dB and the maximum fitted threshold difference was 11.65dB

Conclusions: We suggest that the difference in total light energy between the 3 different target sizes was mainly due to changing properties of retinal spatial summation with many factors.

## 2.2 Introduction

Standard Automated Perimetry (SAP) with a Goldmann size III target (0.43° diameter) is the clinical standard method for measuring visual sensitivity. It has been regarded as the clinical standard method after a series of research papers showed it to be a compromise between the influences of dioptric blur (larger stimuli better)[12], accuracy of result (smaller stimuli better)[13] and effective dynamic range (EDR) (larger stimuli better)[14]. However, even the gold standard size III target can be unreliable. There are many factors that can cause perimetric results to be unreliable: some physiological (pupil size[17, 18] and media opacities[19]) and some variable individual factors (learning effects[15, 16], fatigue[15], foveal and peripheral dioptric blur[12], level of instruction given[20] and both short term[21] and long term

fluctuation[22]). In addition, there is a very real concern around increasing variability of perimetric results as defect depth deepens in patients with glaucoma[23].

In light of this, there have been a number of studies that have recently revisited the relationship between increasing target size and perimetric variability in both glaucoma participants[26-28], and controls[21]. It is thought that spatial summation properties apply when altering target size to determine visual sensitivity. For a stimulus that falls within a receptive field up to 10minutes of arc, the light energy is summed, complete spatial summation occurs and Ricco's Law applies: As target size doubles, the light energy halves to maintain a constant total amount of light energy[32]. As the target size increases to an area greater than that which will fall within the retinal receptive field, incomplete spatial summation occurs, where the product of the target area to a coefficient value of k ($0 < k < 1$) and target luminance maintains a constant total amount of light energy. The value of the coefficient k varies with the degree of spatial summation. This theory is the basis of Goldmann's Law of constancy, which is applied in perimetry and is important when looking at the effect of increasing target size in perimetry.

When investigating the effect of perimetric target size on healthy participants, larger targets (size IV – 0.86° diameter and V – 1.72° diameter) showed less short term fluctuation, but a similar long term fluctuation to the size III target[21]. The authors suggested, therefore, that there would be no benefit in changing target size from the gold standard size III target. However, this was a small study, with a sample of 10 participants and the authors did acknowledge the limitations of the young average age of their study participants (29.1 ± 6.1yrs). There have also been a series of studies that have shown there to be benefits to increasing target size when measuring perimetric threshold in patients with moderate to advanced glaucoma[14, 26-28]. These benefits include increased effective dynamic range (EDR)[14] and reduced variability in areas of greater defect depth[26, 28] coupled with a similar precision of testing between target size III and target size V[27]. Recently, the research was extended to look at the effect of a size VI target (3.44°diameter), compared to a size V and III target across the range of glaucoma severities[30]. The results of this study found the target size V to be most sensitive with size VI being the least sensitive to detecting abnormality.

It is important now to look in greater detail at how increasing target size affects perimetric measurement in controls, extending the research to include a greater number of participants and a wider age-range.

## 2.3 Methods

### 2.3.1 Participants

We tested one eye of 40 healthy participants, recruited from the School of Optometry and Vision Science, University of Waterloo, Canada. The participants, which were stratified by age (10 year bands), had a mean age of 58.9 years and ranged from 41 to 76 years. Eighteen participants were male and 22 participants were female. All participants underwent baseline measurements on both eyes and ocular health screening to ensure they were eligible to be included in the study. These measurements included: Visual acuity, refraction (if needed), perimetric testing using a Humphrey Field Analyzer SITA-Std 24-2 test, optical coherence tomography using the Cirrus Optical Coherence Tomographer; Carl Zeiss Meditec, intraocular pressure measurement by Goldmann applanation tonometry and a fundus photograph. Participants were included if the study eye had a refractive error equal to or less than 5DS and 2.50DC with a best corrected visual acuity of 6/9 or better. They were excluded if they had any history of ocular surgery, or trauma, or any ocular/ systemic disease that could affect the visual field outcome in the study eye. They were also excluded if they had a diagnosis of amblyopia in the non-study eye. If both eyes were eligible for the study, the right eye of odd-numbered participants and the left eye of even-numbered participants were enrolled.

### 2.3.2 Visual Testing

Since all participants were naïve perimetry observers, each participant attended 2 study visits, no more than 90 days apart. The first visit served as a practise visit where the participants were familiarized with the visual field testing in order to mitigate learning effects. At each visit, 3 perimetric tests, each with a different target size, were carried out on the study eye using appropriate near refractive correction as defined by the perimeter. All perimetric testing was carried out using Standard Automated Perimetry, 24-2 full threshold with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec). The stimulus sizes used for the 3 tests at each visit were Goldmann stimulus size III (0.43° diameter, $4mm^2$), size V (1.72° diameter, $64mm^2$) and size VI (3.44° diameter, $256mm^2$) respectively. The order of the visual field tests was randomised for each participant, but maintained for the second study visit. A minimum rest break of 5 minutes was given between tests. Tests were repeated if the false positive rate was greater than or equal to 15%. In addition, 3-dimensional imaging of the optic disc and macula was performed using the Cirrus high definition optical coherence tomographer (Cirrus HD-OCT; Carl Zeiss Meditec) for both eyes on the first visit and the study eye on the second visit.

### 2.3.3 Statistical Analysis

As the first visit was a practise session, we analysed only the second visit perimetry results for each target size. We removed all blindspot locations (co-ordinates (15,3) and (15,-3) for OD and (-15,3) and (-15,-3) for OS) and, at the locations where 2 threshold readings were measured, we used the second measurement. To assess the interaction between the 3 different target sizes, we took each participant's average threshold (over the entire field in decibels) and converted the value to candelas (measurements converted from decibels (dB) to apostilbs (asb), from asb to candelas per square metre ($cd/m^2$) and finally from $cd/m^2$ to candelas (cd) – equations in appendix[A]). This conversion was carried out in order to obtain a linear scale and total light energy for each target size, eliminating spatial summation effects. We then regressed these average thresholds (in both dB and cd) against age for each target size To compare the difference in total light energy between the target sizes, we took the minimum and maximum fitted difference between the target sizes in cd and converted the values back to size III dB to give a meaningful value.

## 2.4 Results

When measured in dB, figure 2-4-1 shows that, as target size increased, average threshold also increased (light intensity decreased). Based on spatial summation properties and Goldmann's law of constancy, we would anticipate that, when converted to total light energy (threshold in cd), the luminous intensity for each target size would be equivalent. However, figure 2-4-2 shows that as target size increased, total light energy also increased. Table 1 outlines the minimum and maximum average fitted threshold differences, calculated in size III dB, between each target size when the thresholds were converted to cd (values based on robust fit). The threshold difference varied between 4.68 and 11.65 size III dBs. The largest difference was between the size III and size VI target, but there was a noticeable difference between all fitted values. Additionally, when the data was plotted by concentric zone for the 3 target sizes (central 10°, 10-16° and 16-24° ), figure 2-4-4 shows that this trend held true within each concentric zone. Furthermore, figure 2-4-2 shows that the difference between average fitted thresholds (total light energy in cd) increases with age, especially for the size VI target. When fitted by age, figure 2-4-3 shows that, up to the age of 65 yrs, the fitted threshold difference in cd (total light energy) between the 3 target sizes was linear. As age increased above 65yrs, we can see that there was a stepwise increase in average threshold for all 3 target sizes. When using a robust fit, the difference in total light energy was still constant between target size III and V, but there was a slight increase in fitted difference as age increased between target size III and VI and target sizes V and VI

When comparing inter-individual variation, the size III target showed the greatest inter-individual variation when average threshold was measured in dB (figure 2-4-1). However, when converted to total light energy (threshold in cd), the size III target had the least inter-individual variation and the size VI target showed the greatest inter-individual variation (figure 2-4-2). Size V inter-individual variation was similar when measured in dB and when converted to cd.

Finally, we also measured the actual size of each of the targets as displayed in the HFA (table 2). We found all the stimuli to be very slightly smaller than the expected area. This decrease in area was between 3.02% and 5.04% smaller than the expected measurement.

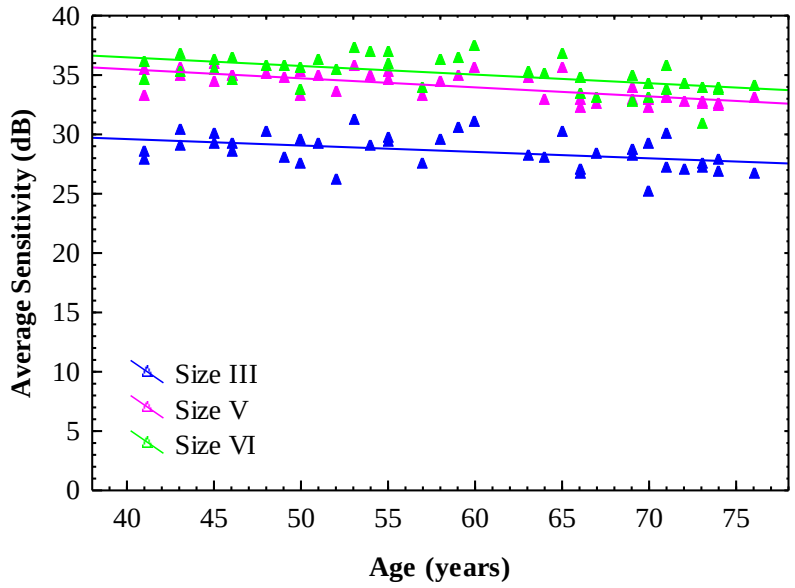



**Figure 2-4-1: Graph to show comparison of full field average perimetric sensitivities for size III, V and VI targets in decibels**

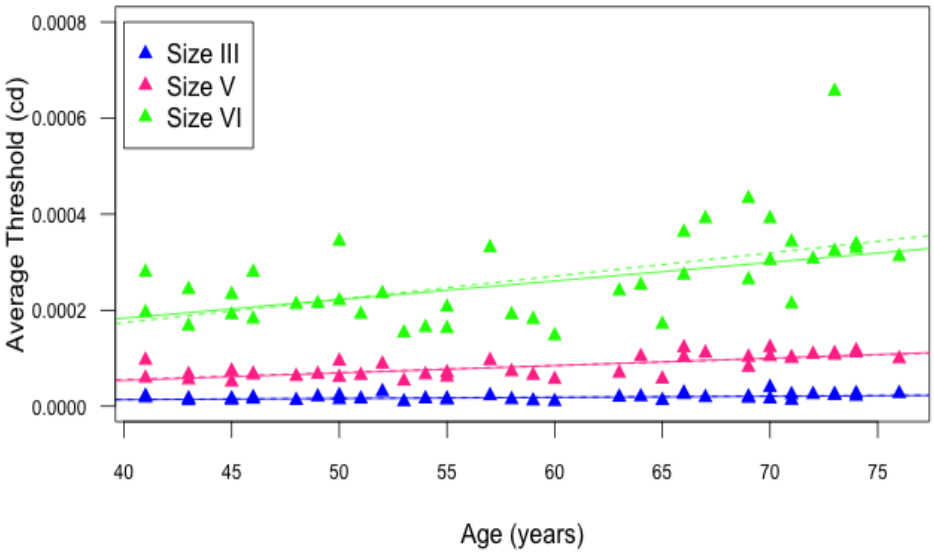



**Figure 2-4-2: Graph to show comparison of full field average perimetric thresholds for size III, V and VI targets in candelas (regular fitting; dotted line, robust fitting; solid line)**

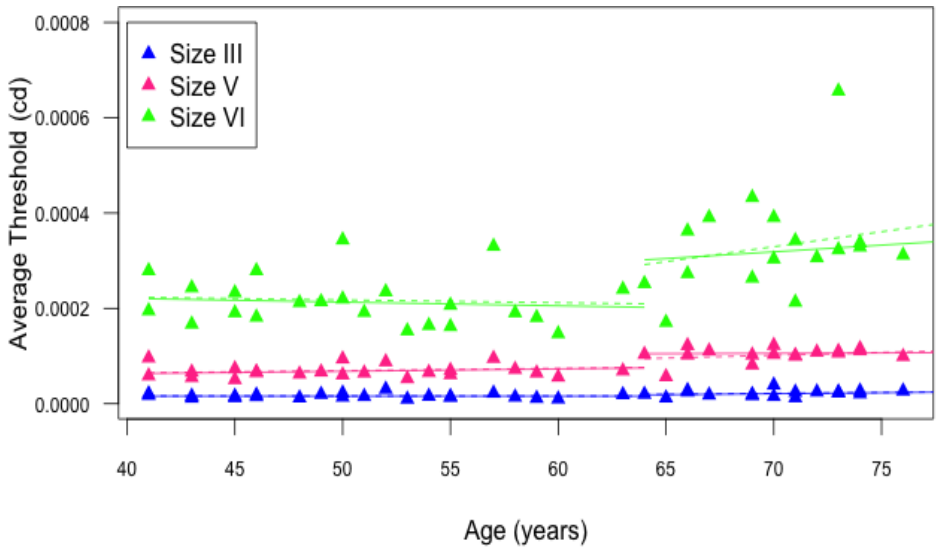



**Figure 2-4-3: Graph to show optimal linear fits of full field average perimetric thresholds for size III, V and VI targets in candelas for the both participants under 65yrs , and over 65yrs (regular fitting; dotted line, robust fitting; solid line)**

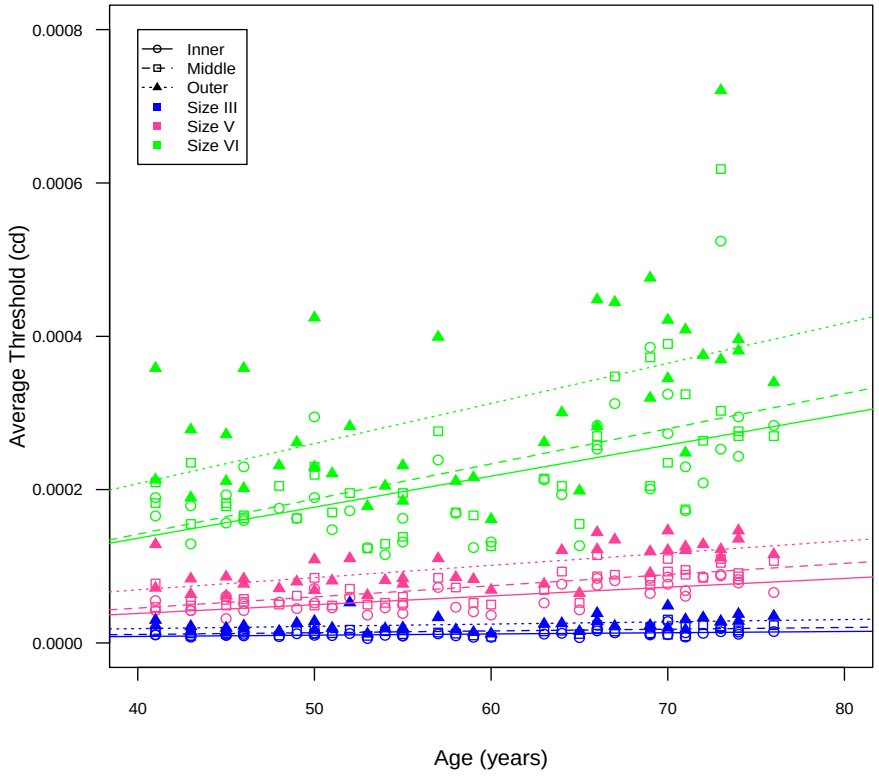



**Figure 2-4-4a: Graph to show comparison of average concentric zone perimetric threshold for III, V and VI targets in candelas**

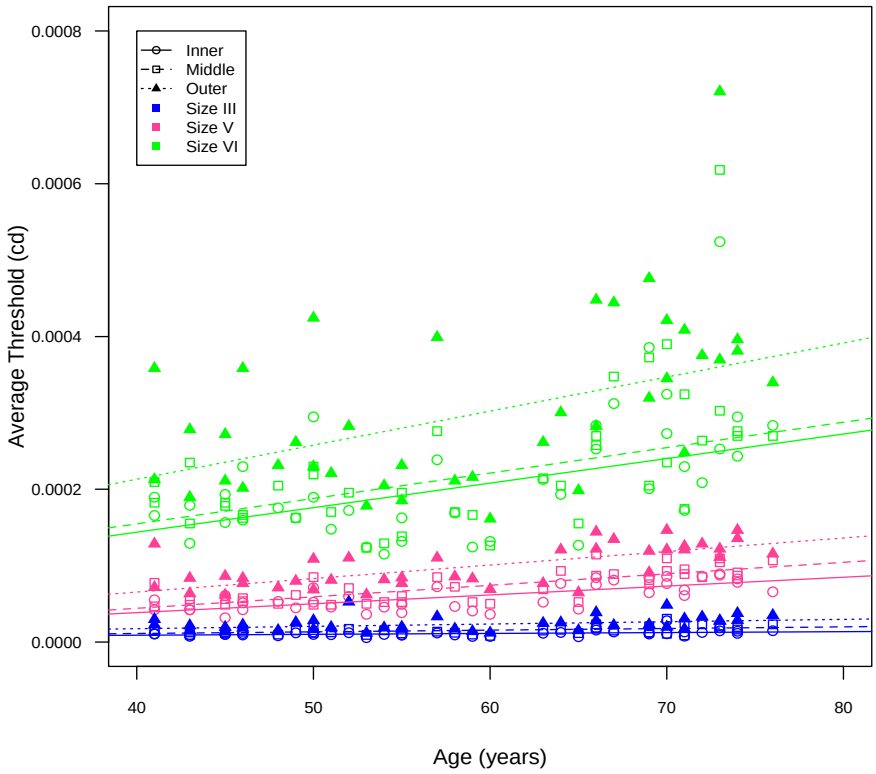



**Figure 2-4-4b: Graph to show robust fitting for the comparison of average concentric zone perimetric threshold for III, V and VI targets in candelas**

| | Target sizes | Difference (in size III dB) |
|---|---|---|
| Difference @ 41yrs of age | III to V | 5.96 |
| | III to VI | 11.25 |
| | V to VI | 5.28 |
| Difference @ 76yrs of age | III to V | 6.97 |
| | III to VI | 11.65 |
| | V to VI | 4.68 |

**Table 1: Table corresponding to figure 2-4-2 to show the difference, in size III dBs, between the robust fitting for each target size taken at 41 yrs and at 76 yrs where the difference was minimum and maximum, respectively, in cd.**

| Area ($mm^2$) | | | | | |
|---|---|---|---|---|---|
| Target size III | | Target size V | | Target size VI | |
| Projected | Actual (mean average of 3, % decrease from expected) | Projected | Actual (mean average of 3, % decrease from expected) | Projected | Actual (mean average of 3, % decrease from expected) |
| 4 | 3.81, 4.75 | 64 | 60.77, 5.04 | 256 | 248.26, 3.02 |

**Table 2: Table to show the expected and actual measurements of the HFA target sizes on the HFA perimeter that we used for the study**

## 2.5 Discussion

When considering average full field perimetric threshold in dB, our study shows that as target size increased, stimulus intensity decreased (figure 2-4-1). These results seem to agree with the spatial summation theory (Ricco's Law of energy conservation)[32]. However, when these values were converted to total light energy (threshold in cd), thus removing the effects of spatial summation, we found there to be an increase in average threshold value (figure 2-4-2). We are aware that the dB threshold values can only be as accurate as 0.5dB due to the increment step size of the HFA. This 0.5dB value varies over the range of light intensities once converted to a linear scale. However, at 30dB, a 0.5dB difference is $1.382 \times 10^{-6}$cd, which is a considerably smaller value than any difference between fitted values in figure 2-4-2. Therefore, we can ascertain that there is an actual difference between the light intensities of the different target sizes, even when removing the effects of spatial summation.

We can speculate on the reasons that these differences in total light intensities may occur between target sizes. Firstly there are potential errors that may cause this discrepancy between the values: Calibration of the HFA may have initially been miscalculated, or the apertures in the target wheel may have been misjudged at production. In this case, we would expect the size V and VI apertures to be too small (participants would be observing the light to be too bright – the smaller the aperture the brighter the target would be seen due to the spatial summation theory). When measuring the actual stimulus sizes, as displayed by the HFA, we found the target sizes to be only very slightly smaller than expected (values in table 2). Since the size differences between expected and actual are minimal, and since the size III target was also slightly too small, this in itself cannot wholly account for the difference in total light energy we found between the target sizes. Furthermore, we also found a

slightly greater difference in the total light energy with increasing age between the size III and V target and the size III and VI target (figure 2-4-2). Figure 2-4-3 shows that there was a stepwise increase in average threshold as age increased to 65yrs. This suggests a further reasoning behind the difference between target sizes.

Another explanation could be due to the characteristics of spatial summation, and therefore, Goldmann's theory of energy conservation, changing across the retina. Goldmann perimetry, where Goldmann's law of energy conservation was originally formed is a kinetic perimetry test measuring visual sensitivity of the peripheral retina. Conversely, the HFA-FT perimetry testing we used in this study is a static perimetry test and only measures the central 24° of the visual field.

We know that in some areas of the retina there is complete spatial summation (when a stimulus of less than 10 minutes of arc falls directly in a receptive field). However, when the stimulus exceeds the size of the receptive field, incomplete spatial summation occurs[32]. Goldmann's Law of energy conservation applied in perimetric testing is defined by the following equation:

$$A^k \times L = C$$

Where: A= area of target ($mm^2$); k= coefficient between 0 and 1 indicating whether spatial summation is complete or incomplete (dependent on many factors), where 1= complete spatial summation and 0= incomplete spatial summation; L=luminance of target (asb); C=constant [40]

The accepted value of k for perimetric testing is a constant value of 0.8. However, we know that the degree of spatial summation changes with many factors, thus in reality, the value of the coefficient k is far from constant. It is known that the extent of spatial summation changes with eccentricity[36]. Dannheim also confirmed that the value of k changes as target size differs. Furthermore, across individuals, the shape of the spatial summation curves change, showing that the value of k not only differs within individuals, but also between individuals[36]. Another paper demonstrated a change in spatial summation properties in the parafoveal retinal area, likely explained by age-related loss of retinal ganglion cells and subsequent re-organisation of the receptive fields[38]. Since our study encompassed both change in target size and many participants of the older generation, it is highly likely that the value of the coefficient k differed not only across participants, but also within participants. This in itself could have caused the unexpected difference in total light energy between target sizes.

If we take the current value of the coefficient k used for the size III target to be correct (where k=0.8), we can calculate the expected values of k for the size V and VI targets, based on an expected, known area for each stimulus. This can be calculated for age below 65yrs (since, when converted to

cd, we know that the threshold step change in cd is constant between the 3 different target sizes, thus the value of k will also be constant across this age range within target size). Using the fitted threshold values, where threshold is measured with a linear scale (asb), and applying Goldmann's Law of Energy Conservation (p21), the following k values are established: For the size V target, k = 0.6, for the size VI target, k = 0.5. Where age increases above 65yrs, k is clearly affected to a greater degree and with an inconsistent step change.

Conversely, if we take the value of the coefficient k to be 0.8 and assume that it is correct across all target sizes, we can calculate the resulting area of target sizes (if the size III target is taken to be $4mm^2$). Using Goldmann's law of energy conservation (on p21), the following areas are established: Size V target = $21.5mm^2$, Size VI target = $29.1mm^2$.

Therefore, if the value of k was taken to be correct at 0.8 across all target sizes, and the difference in total light energy was due to engineering/calibration error, the size of the stimuli would have to be a great deal smaller to compensate (as shown above). Since the actual areas of all the stimuli were only slightly smaller than the expected measurements (table 2), the difference in total light energy we found between the 3 different target sizes is likely mainly due to the changing value of the coefficient k across target sizes. The reality that all the stimuli are very slightly too small (and to a very similar degree) could account for an overall increase in total light energy, but could not account for the overall difference between the target sizes.

The difference in inter-individual threshold variability found between target sizes in this study is also interesting. Gilpin et al.[21] looked at the effect of increasing target size on perimetric variability, although thresholds were only analysed in dB. They found larger target sizes (size V and VI) to have greater inter-individual variation. In our study, we found target sizes V and VI to have lower inter-individual variability when measured in dB (figure 2-4-1), but size VI to have the largest inter-individual variation when measured in cd (figure 2-4-2). The difference between our findings and Gilpin et al's results is likely due to Gilpin's study being performed on a smaller sample of younger participants. We also found target size V to have the most stable inter-individual variability when thresholds are converted from dB to cd.

Based on our results, target size V seems to have benefits over the gold standard target size III when used to measure visual sensitivity in normals, since it has the lowest inter-individual variability when thresholds are measured in dB and converted to total light energy (cd). However, SAP III is the current gold standard method of perimetry measurement due to it being a compromise between the influences of dioptric blur[12], accuracy of result[13] and effective dynamic range (EDR)[14] and the value of

the coefficient k is based upon these gold standard conditions (currently taken as k=0.8). However, since we know that the value of k changes both between and within participants as factors such as age and target size vary, there must be further work to verify the adjustment needed for k as these factors change to ensure equality of total light energy across the targets sizes.

In summary, our research shows that increasing target size does not give equality of results, even when converted to total light energy and this inequality increases as age increases above 65yrs. If the target sizes are accurately calibrated then it is likely due to the changing value of the coefficient k (determinant of the completeness of spatial summation in any given situation). The stimuli being slightly too small may also account for some overall increase total light energy. Therefore, before another target size is deemed as a rival for the current gold standard, there must be further research to ensure the stimuli are accurately calibrated and verify the optimum value of k for each stimulus size, by eccentricity and age.

# Chapter 3

# The Effect of Increasing Target Size on the Detection of Abnormality in Very Early Glaucoma

Sarah L. Bishop, Natalie Hutchings, John G. Flanagan

## 3.1 Overview

Purpose: To investigate the effect of increasing target size on the measurement of visual sensitivity in very early glaucoma.

Methods: Seventeen participants with very early glaucoma (perimetric mean deviation of equal to, or better than, -4.0dB) were recruited and 3 full threshold visual field tests were performed on one study eye of each participant using 3 different target sizes, at 2 separate visits (no more than 90 days apart). We compared the normal and abnormal test locations between SITA-Std and the full threshold target sizes III (0.43° diameter), V (1.72° diameter) and VI (3.44° diameter) by computing empirical probability plots for each participant and target size (normal percentile limits defined from normal data in chapter 2). We then compared the number of normal and abnormal test locations at each defect depth (5%, 2%, 1% and 0.5%) between SITA-Std and the 3 different target sizes using repeated measures analysis of variance.

Results: We found there to be no notable difference in amount or location of defect between SITA-Std and the size III full threshold perimetric testing, confirming equivalence in the tests. We also found there to be no difference in number of abnormal points between SITA-Std and the 3 different target sizes ($p = 0.066$). However, the locations of abnormal points for the largest size VI target were not found to be correlated well with those of SITA-Std.

Conclusions: Our results suggested that, although there was statistically no difference in the number of abnormal points detected with the larger target sizes, the size VI target was not as sensitive as SITA-Std due to a discrepancy between the locations of abnormal points detected.

## 3.2 Introduction

Functional progression of glaucoma, across all stages, is routinely monitored by using the Standard Automated Perimetry, size III target (SAP III – 0.43° diameter, 4mm$^2$). This is the gold standard perimetric measurement, since it was shown to be a compromise between the effects of peripheral

dioptric blur[12], accuracy of result[13] and effective dynamic range (EDR)[14]. However, there is literature that shows perimetric accuracy with a size III target to decrease notably as defect depth increases[22, 23]. In light of this, there have been a number of research papers that have investigated ways to increase the accuracy and precision when measuring functional defect in glaucoma. Recently, the relationship between increasing target size and measurement of visual fields has been re-examined in participants with glaucoma. This literature has shown many benefits to increasing target size up to a size V target (1.72° diameter, 64mm$^2$). These benefits include decreased variability as defect depth increases[26, 28] and greater EDR[14]. There is also literature showing the precision of testing to be similar between the gold standard size Goldmann III target and the larger Goldmann size V target[27]. Recently a paper looked at the effect of a size V and VI Goldmann (3.44° diameter, 256mm$^2$) target on the measurement of visual fields in participants with all stages of glaucoma[30]. This research showed that target size V had a slightly better sensitivity to detecting abnormality in glaucoma patients, both across the range of severities and in relatively early defect.

When using Goldmann target sizes, Goldmann's Law of constancy is applied (based on Ricco's Law of spatial summation): Within a given area below 10 (Ricco's area), the total light energy needed to produce a response (area to the power of a coefficient k multiplied by luminance) is constant[40]. The value of the coefficient k varies between 0 and 1, depending on the degree of spatial summation. Ricco's area has been shown to increase in the periphery of a healthy retina for both s-cones and l-cones[33]. The literature also suggests that Ricco's area increases, due to loss of retinal ganglion cells, (RGCs) in both age[38] and in glaucoma[35], to maintain a similar number of RGCs in a receptive field. Redmond et al.[35] suggested that the larger targets are able to still fall within Ricco's area and be detected by a greater number of 'healthy' RGCs, resulting in a more reliable result with a larger target size.

Increasing target size has largely been shown to be of benefit when measuring visual sensitivity in glaucoma[14, 26-28], although there is question as to whether increasing further to a size VI is detrimental to the sensitivity of the perimetric test[30]. However, previous research has mostly been performed using participants with moderate to late stage glaucoma, and must be extended to looking at the very early stage of the disease. This study will investigate the effect of target size III, V and VI on the measurement of visual sensitivity in the very earliest stages of glaucoma.

## 3.3 Methods

### 3.3.1 Participants

One eye of 17 participants, with very early glaucoma, was tested. All types of glaucoma were included, as long as treatment had been started. These participants were recruited from the Ocular Health Clinic of the School of Optometry and Vision Sciences, University of Waterloo, Canada and from Optometry and Ophthalmology Offices in Kitchener-Waterloo, Ontario. The glaucoma participants had a mean average age of 63.2 years and ranged from 48 years to78 years. Nine participants were male and 8 participants were female. The participants were stratified into 4 groups according to mean deviation (MD), where MD was better than -2dB, measured by the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec), with an additional MD group between -2dB and -4dB. In addition, participants were required to have a refractive error equal to or less than 5DS and 2.50DC with a best corrected visual acuity of 6/9 or better. They were excluded if they had any history of ocular surgery, or trauma, or any ocular/ systemic disease that could affect the visual field outcome, other than glaucoma, in the study eye, or a diagnosis of amblyopia in the non-study eye. All participants were experienced in perimetry testing.

### 3.3.2 Visual Testing

Each participant attended 2 study visits, where the first visit served as a practice to mitigate learning effects. The visits were no more than 90 days apart. At each visit, 3 perimetric tests, each with a different target size, were carried out using appropriate near refractive correction, as defined by the perimeter. All perimetric testing was carried out using Standard Automated Perimetry, 24-2 full threshold with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec). The stimulus sizes used for the 3 tests at each visit were Goldmann stimulus size III (0.43° diameter, $4mm^2$), Goldmann size V (1.72° diameter, $64mm^2$) and Goldmann size VI (3.44° diameter, $256mm^2$) respectively. The order of the visual field tests was randomised for each participant, but maintained for the second visit. A minimum rest break of 5 minutes was given between tests. Tests were repeated if the false positive rate was greater than, or equal to, 15%. In addition, 3-dimensional imaging of the optic disc and macula was performed using the Cirrus high definition optical coherence tomographer (Cirrus HD-OCT; Carl Zeiss Meditec) for both eyes on the first visit and the study eye on the second visit.

### 3.3.3 Statistical Analysis

As the first visit was a practise session, we used the second visit perimetry results for each target size. All blindspot locations were removed (co-ordinates (15,3) and (15,-3) for OD and (-15,3) and (-15,-3) for OS) and, at the locations where 2 threshold readings were measured, we used the second measurement. To establish the limits of normality for each full threshold target size we used normal data collected from 40 participants (Chapter 2) to determine percentile limits for each location (52 locations) and target size (3 target sizes). We then plotted the thresholds for the participants with early glaucoma for each location (in decibels - dB). From these graphs, we determined normal and abnormal locations, taking defect depth into consideration, for every participant (n=17) and all stimulus sizes. We then computed empirical probability plots for all participants and all target sizes. We also compared the results to the SITA-Std plots obtained at recruitment. A repeated measures analysis of variance (rANOVA) was used to compare the number of normal and abnormal test locations detected by SITA-Std and each of the 3 target sizes at each defect depth across participants.

## 3.4 Results

Figure 3-4-1 (A-D) shows an example of the empirical probability plots computed to compare the normal and abnormal locations between SITA-Std and all target sizes for each participant (see Appendix for all plots). When comparing the probability plots of the SITA-Std and the 3 different full threshold Goldmann target sizes (target size III, size V, size VI), we found there to be no significant difference in the number of normal or abnormal test locations (5%, 2%, 1% and 0.5% deviations from normal) across target sizes (rANOVA; Target Size*Abnormality $F_{(12,\ 240)}$=1.708, p=0.066; Figure 3-4-2). The empirical probability plots also show that SITA-Std and the size III full threshold detected defects in similar locations for each participant, since 78% of the time (mean average; range of 63% to 96%), both size III perimetric tests detected equivalent locations as normal or abnormal for a single participant (see figure 3-4-3). Since there was no difference between the number of normal and abnormal locations detected, and since these locations are similar, we can confirm that the SITA-Std database and the calculated full threshold size III tests are comparable.

Although the statistical tests showed that there was no significant difference in the detection of visual sensitivity when using the larger target sizes compared to the current gold standard size III target, the empirical probability plots showed an important clinical observation that must be taken in to account. When comparing the distribution of abnormal locations across the visual field, SITA-Std

and size III full threshold detected similar abnormal locations (see figure 3-4-3). The size V target appeared to detect abnormal locations that were altogether similar to SITA-Std, although there were a few cases where the abnormal locations were not sufficiently comparable. When comparing the size VI target to SITA-Std, in some cases, the VI target detected more abnormal locations than SITA-Std (e.g. participants 211 and 216) and in some cases, the larger target detected less abnormality (e.g. participants 207 and 210). There were a few cases were size VI detected generally scattered points compared to SITA-Std (e.g. participants 203 and 214). Despite size VI detecting a similar number of abnormal locations statistically, when observing the empirical probability plots, the distribution of abnormal locations for the majority of participants was inconsistent compared to the SITA-Std results (current clinical standard). Table 3 shows the 3 target sizes for each participant ranked in order of how similar each empirical probability plot appeared to SITA-Std. Overall, the size VI target showed the most inconsistency to the SITA-Std abnormal locations based on the ranking scores (table 3), while the full threshold size III and size V targets were, in comparison to SITA-Std, ranked similarly.

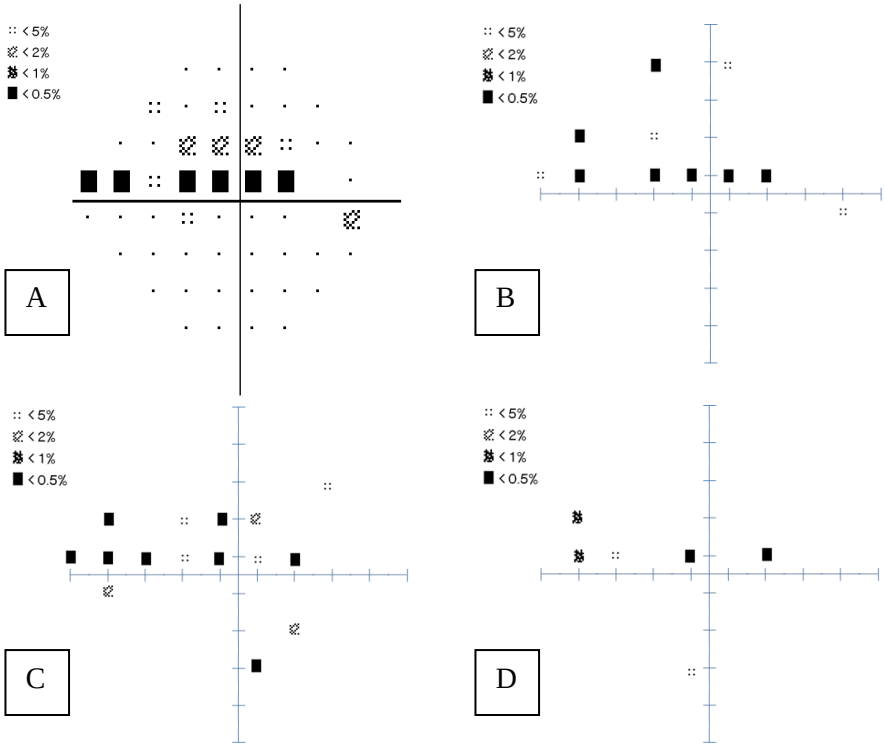



**Figure 3-4-1: Example of empirical probability plots showing good agreement between SITA-Std and full threshold size III for participant 207 (OD) using: A: SITA-Std size III, .B: Full threshold size III, C: Full threshold size V, D: Full threshold size VI**

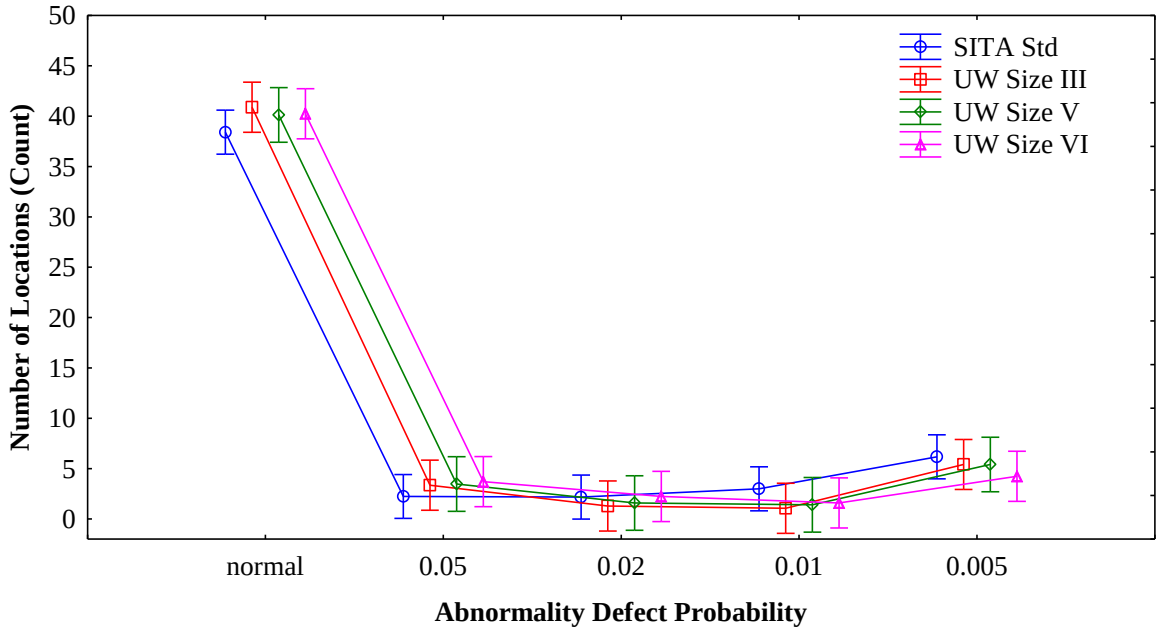



**Figure 3-4-2: Interaction of target size and defect depth across early glaucoma subjects (rANOVA Target Size*Abnormality). There was no significant difference between target sizes across defect depths.**

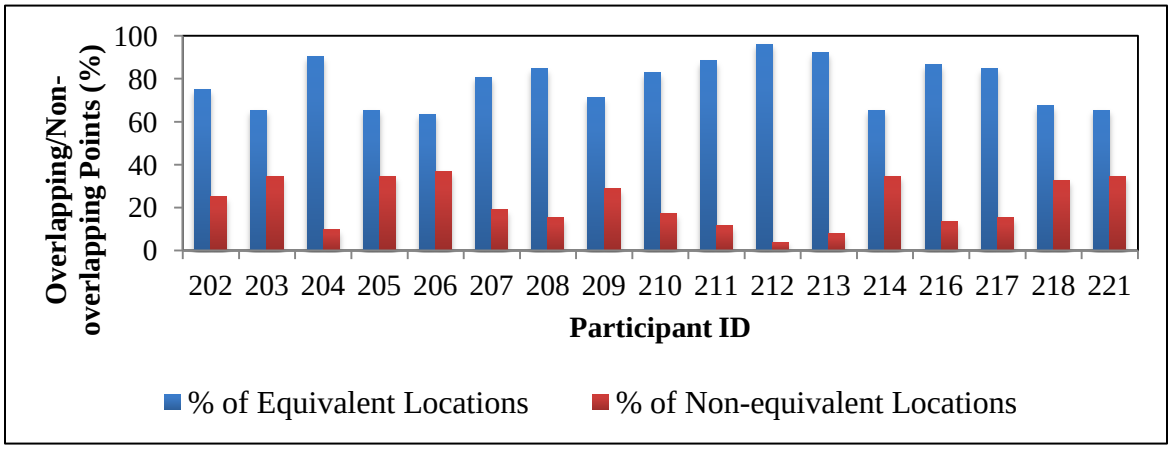



**Figure 3-4-3: Bar graph to show percentage of equivalent and non-equivalent locations between SITA-Std and size III full threshold visual fields. Measured as equivalent if both fields had an abnormal point or both fields had a normal point in the same location.**

| Participant | Ranked score of target size (based on similarity of abnormal locations to SITA-Std | | |
|---|---|---|---|
| | III | V | VI |
| 202 | 2 | 3 | 1 |
| 203 | 1 | 2 | 3 |
| 204 | 1 | 2 | 3 |
| 205 | 2 | 1 | 3 |
| 206 | 1 | 2 | 3 |
| 207 | 1 | 2 | 3 |
| 208 | 3 | 2 | 1 |
| 209 | 2 | 1 | 3 |
| 210 | 1 | 2 | 3 |
| 211 | 1 | 2 | 3 |
| 212 | 1 | 2 | 3 |
| 213 | 3 | 1 | 3 |
| 214 | 1 | 2 | 3 |
| 216 | 2 | 1 | 3 |
| 217 | 1 | 2 | 3 |
| 218 | 3 | 2 | 1 |
| 221 | 1 | 2 | 3 |
| **Total score** | **27** | **31** | **45** |

**Table 3: Table to show the ranked scores, for how similar the empirical probability plot appeared in relation to SITA-Std (where 1 = most similar and 3=least similar), based on locations of abnormality, for each participant**

## 3.5 Discussion

The full threshold size III test detected a similar number and location of normal and abnormal points to SITA-Std size III, confirming that these databases were essentially equivalent. Our results also suggested that the number of abnormal points detected was similar across SITA-Std and the full threshold size III, size V and size VI targets in the early glaucoma group. However, we can confirm that there was a clinical difference in the distribution of abnormal points between the SITA-Std and full threshold size VI target by observing the empirical probability plots. While the full threshold size III and size V targets detected a similar number of abnormal points, the size VI target was not always able to detect the extent of abnormality in these early glaucoma participants. Sometimes the size VI target also detected points that were much more scattered than the clinical standard.

We know from previous literature that there are advantages to using a size V target to measure functional defect in moderate to advanced glaucoma; namely a larger EDR[14], decreased

variability[26, 28] and a slightly greater degree of repeatability when measuring perimetric mean deviation[29]. Wall et al also showed that there was a similar precision of testing between the size III and size V target for the later stages of glaucoma[27]. Our results suggest that there is also a similar precision of testing between a size III and size V target when measuring functional defect in the very early stages of glaucoma.

We also determined the number of abnormal test locations detected in the very early glaucoma participants with a larger size VI target. Our results showed that, statistically, we identified a similar number of abnormal points with a size VI compared to a size V or size III target. These results suggested that there was no disadvantage to increasing target size even further. This, however, is surprising, since Bek[13] showed the larger the stimulus, the more relative the scotoma measured. This difference in results could have been due to the fact that Bek used the blindspot as an absolute scotoma while we used participants with known visual field defects due to glaucoma. However, although statistically the size VI target seemed to detect a similar number of abnormal points as SITA-Std, the larger target size did not always accurately match the spatial location of SITA-Std and, therefore, was considered not as sensitive clinically as the current standard (table 3) as it may lead to a different interpretation of the visual field defect.

Recently Wall et al.[30] also investigated the effect of increasing target size to a size VI when measuring visual sensitivity in patients with a range of glaucoma severities, although the authors mainly focused on participants with moderate to advanced glaucoma. They found that full threshold perimetric testing with a size V target was the most sensitive to detecting visual loss in the glaucoma participants across the full range of severities. They also found that the larger size VI target was too large to detect the full extent of abnormality in these patients. They suggested that the lower sensitivity they found was due to the larger target sizes being partly viewed across the steep borders of the moderate/advanced glaucomatous scotomas. This theory could also explain the difference between our findings and the findings of Wall et al. when looking at the number of abnormal locations. All of our participants were included in the study as a result of their very early glaucoma (MD equal to, or better than, -4dB). In very early glaucoma the scotomas are generally much more relative and the borders are less steep. We suggest that, with the shallower borders it is possible that the size VI target is less likely to be viewed at these borders (i.e. no steep cut off point), which may cause the size VI target to be detected at the same number of spatial locations, or even overestimate the defect in very early glaucoma compared to SITA-Std (e.g. participants 211 and 216). Another possibility is that the visibility of the target would not be significantly impacted with the shallower

defect, leading to underestimation of the defect (e.g. participants 207 and 210). Additionally, because of the early defect in our study, some participants displayed functional visual sensitivity close to normal (e.g. participants 208 and 212). In this case, SITA-Std and the full threshold targets all measured isolated, spurious defects in different locations. This would lead to a similar number, but different locations of abnormal points being detected with each target size.

Although we found that there was no statistical difference in the number of abnormal locations detected between the size III, V and VI targets, we can conclude that the size VI target was less able to detect abnormality accurately and precisely in very early glaucoma compared to the clinical standard.

# Chapter 4: Conclusion

The aim of our research was to investigate the effect of increasing target size on the perimetric results in both normals and in early glaucoma. Since there are no current normative limits for the larger target sizes V (1.72° diameter) and VI (3.44° diameter), we firstly used 40 normal participants (aged 40-80yrs) to define normal percentile limits by age and eccentricity for all target sizes (III, V and VI). We used these limits to identify abnormality in the early glaucoma group. Subsequently, we computed empirical probability plots for each of the 17 early glaucoma participants and compared the amount of defect between SITA-Std and the 3 target sizes using a rANOVA.

We found there to be no significant difference between the number of abnormal points detected with SITA-Std and the 3 target sizes ($p=0.066$), suggesting that there is no disadvantage to using a larger target size to measure functional defect in very early glaucoma. We also showed that a similar number, depth and location of abnormal points were detected for SITA-Std and the full threshold size III perimetric test, confirming that these databases were similar (see appendix for all empirical plots and figure 3-4-3). The difference between our findings and those of Wall et al.[30] may have been due to our larger sample of participants with very early glaucoma manifesting more relative scotomas, which either led to overestimation or underestimation the defect. The discrepancy also could have been due to the size VI target sometimes picking up more scattered abnormal points, falsely detecting these as abnormal. Although the size VI target detected a similar number of abnormal locations statistically, suggesting that the size VI was just as sensitive as the size III target, the distribution of abnormal locations had poor spatial agreement between the size VI and SITA-Std (current clinical standard) – see empirical plots in appendices and table 3. Despite the few cases where the abnormal locations were not sufficiently comparable to the SITA-Std abnormal locations with a size V target, comparable abnormal locations were ascertained with most participants. In addition, the size V target manifested the most stable variation when converted from dB to total light energy (cd) in normals, giving the target size another advantage.

In addition to defining the normal percentile limits and comparing the amount of abnormality in the very early glaucoma participants, we also investigated the threshold interaction of the 3 target sizes for normal patients by age. We found an expected difference (due to spatial summation properties), between the average thresholds when measured in decibels. However, when converted to total light energy (threshold in candelas), a difference in threshold between the target sizes remained (as target size increased, light intensity also increased). This difference was constant up to the age of 65 yrs, but increased slightly as age increased over the age of 65yrs when comparing the size III and V

target to size VI. We suggest that this remaining difference between total light energy was mainly due to the changing degree of spatial summation, and therefore changing value of the coefficient of summation value (k). An overall increase in total light energy may also be partly due to the stimuli sizes on the HFA being slightly too small. There are many different variables that influence the spatial summation coefficient value of k, including age[38], eccentricity and target size[36]. If the currently used value of k (0.8) is used taken as true for the size III target, and the HFA is calibrated correctly, we suggest, based on our results, that the size V target would require a k value of 0.6 and the size VI target would require a k value of 0.5. It is probable that the reality of a variable k value with these factors could cause a discrepancy in thresholds.

In summary, we found that, although it appears as though functional defects in very early glaucoma can be equally as well detected with the larger targets as with the current, smaller standard size III target, our results showed that the larger size VI target was not able to accurately detect early defect compared to the current clinical standard visual field measurement (SITA-Std). The size V target does show promise though, in manifesting a similar sensitivity to detecting abnormality, both in amount and location. Our research has also shown that the total light energy for larger stimuli is not equivalent to that of the clinical standard target. This is thought to be due to varying spatial summation factors and, therefore, a changing value of the coefficient k that is not currently taken into consideration. Before a larger target size is used routinely in practice, there must be further research to ensure the stimuli are accurately calibrated and verify the optimum value of k for each stimulus size, by eccentricity and age.

# Chapter 5: Future Directions

Our research has shown that the size V target (1.72° diameter) has a similar precision of testing to the gold standard size III target (0.43°diameter) , although the size VI target (3.44° diameter) is not sensitive enough to detect the location of abnormality accurately. A size V target has been suggested, in the literature, to be an enhanced method of measurement for visual sensitivity in moderate to advanced glaucoma due to its clinical properties of a larger EDR [14] and reduced variability in greater defect depth [26, 28]. Although we have found a similar precision of testing with size III and size V targets in very early glaucoma, further research with a greater number of very early glaucoma participants must be carried out to further verify these conclusions. Additionally, it is worth considering that, although SITA-Std is the current gold standard method of measuring visual sensitivity, it is difficult to determine whether the few extra abnormal locations detected with the size V target convey a greater sensitivity or simply unwanted scatter.

Currently, the coefficient of summation in perimetry is taken to be k=0.8. It is already known that the degree of spatial summation varies across the retina, and with other factors, such as age [38] and target size [36]. Our research agrees with this, and has shown that total light energy with the 3 different target sizes is far from equal when k is taken as a constant value across the different conditions. If a variable target size is to be used as a perimetric tool in the future, the exact values of k must be known as per target size to ensure equality. We have speculated that, if k=0.8 with a size III target, when a size V target is used, k=0.6 and when a size VI target is used, k=0.5. These values must be investigated with a larger sample of normal participants in order to establish these values with greater precision.

# Appendix

**<u>Chapter 2</u> [A]: Conversion of decibels to candelas:**

Decibels to apostilbs:

asb= $(4\text{-dB}/10)^{\log\text{-}1}$ (derivation graph below)

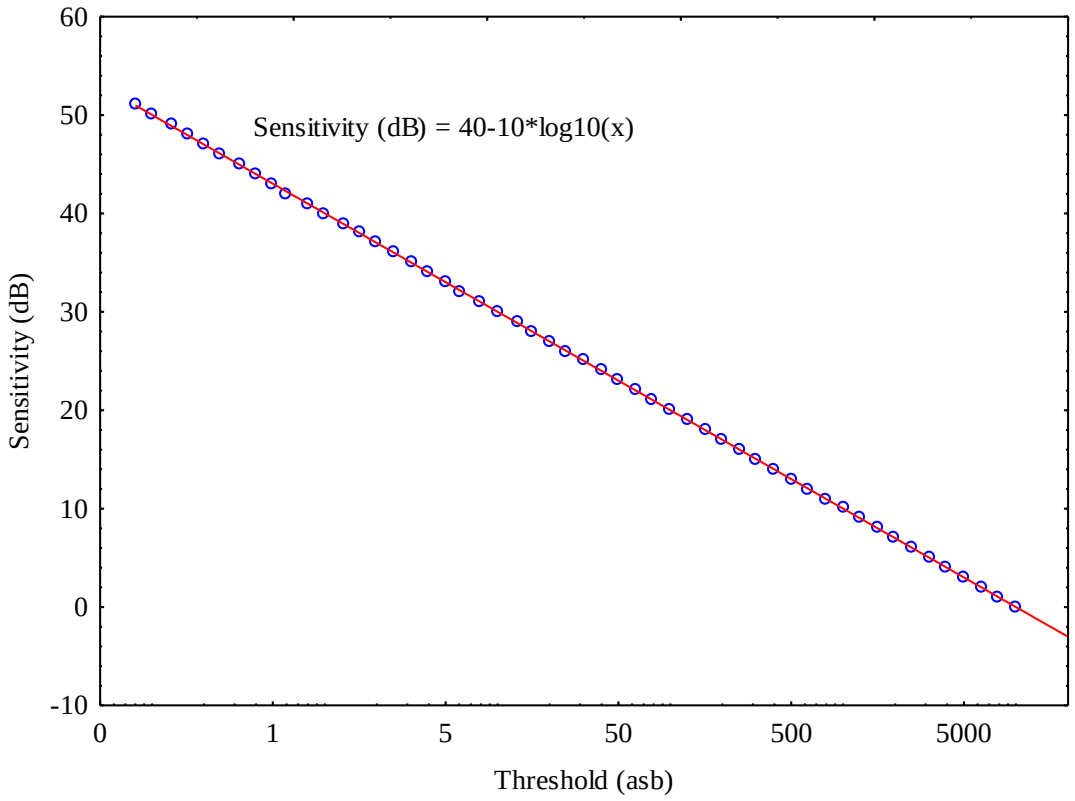



**Figure: Graph to derive the conversion equation of dB to asb when using the conversion values from the HFA handbook. (Humphrey Field Analyzer Hand Book, Table E.1; [41])**

Apostilbs to candelas per square metre: [41]

$cd/m^2 = asb/\pi$

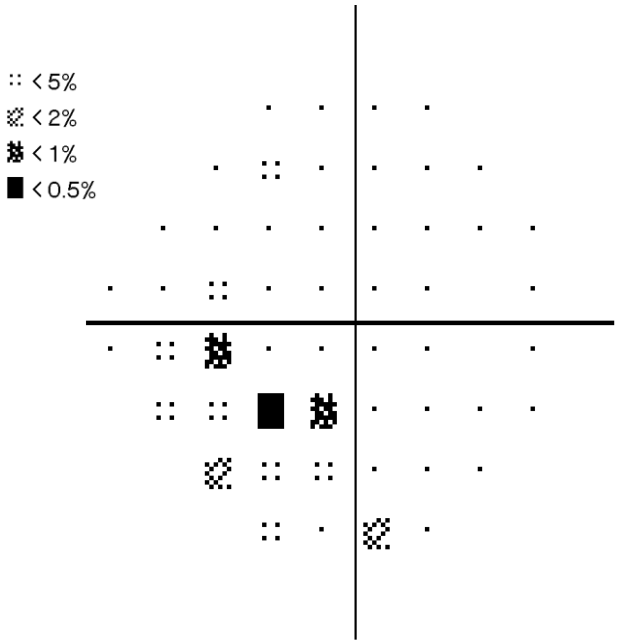
Candelas per square metre to candelas: [42]

Size III: $cd = 0.000004 * cd/m^2$

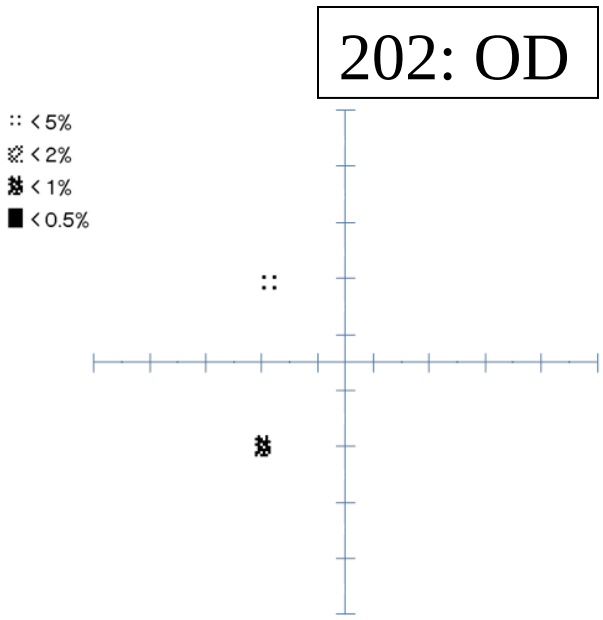
Size V = 0.000064 * $cd/m^2$

Size VI = 0.000256 * $cd/m^2$

**<u>Chapter 3:</u> Empiral probability plots for study eye of all 17 participants**




SITA-Std Size III

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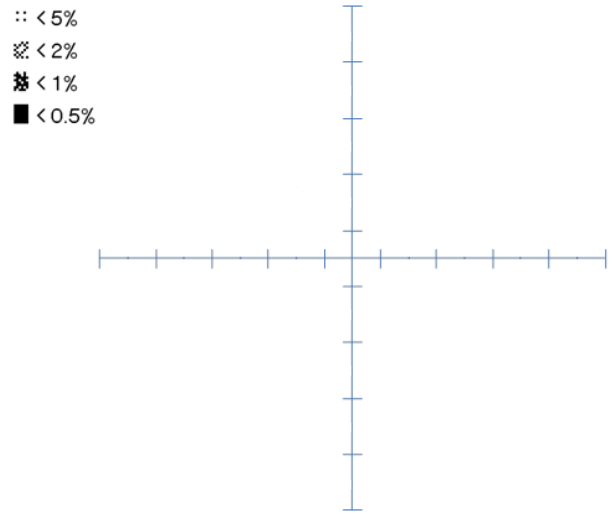


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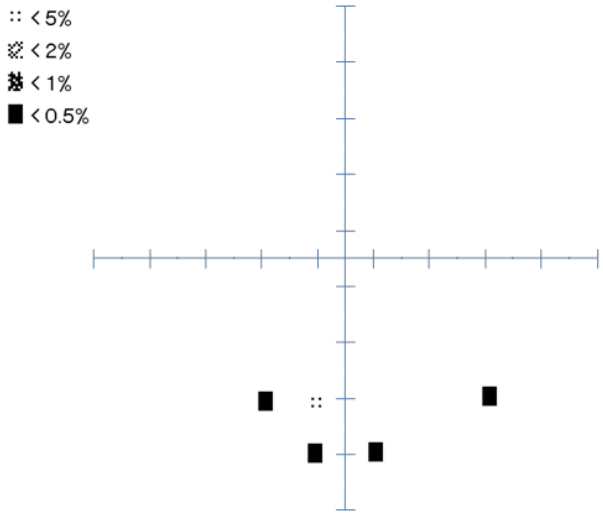


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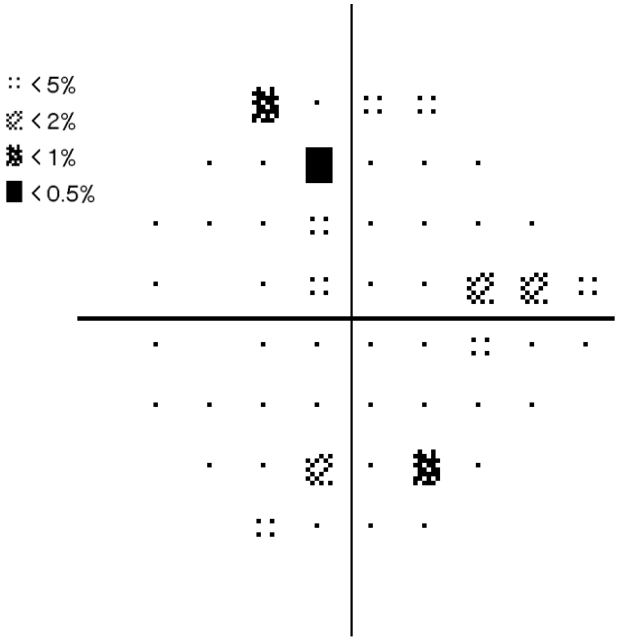


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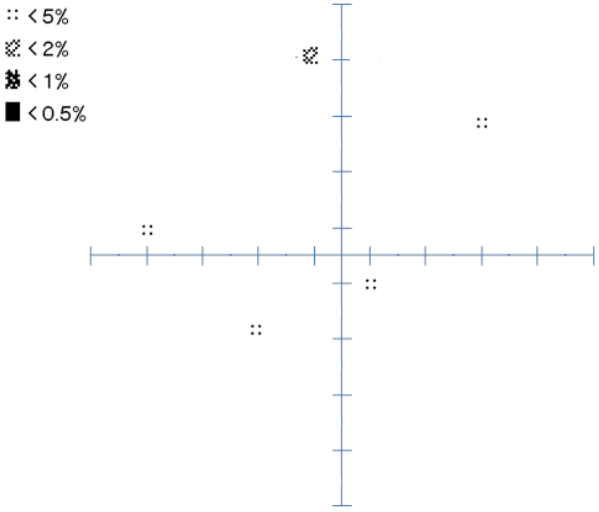


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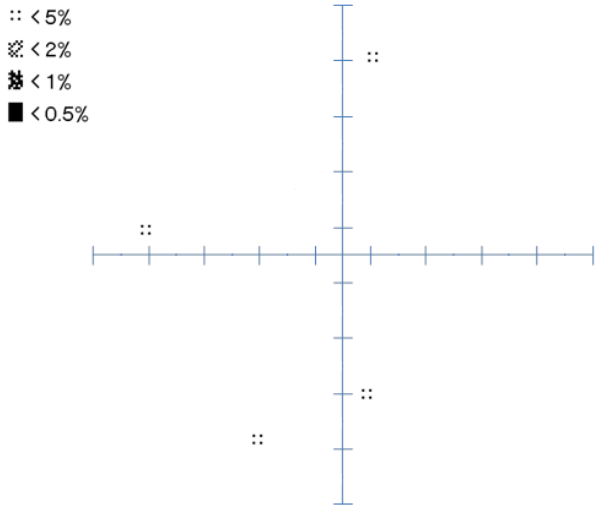


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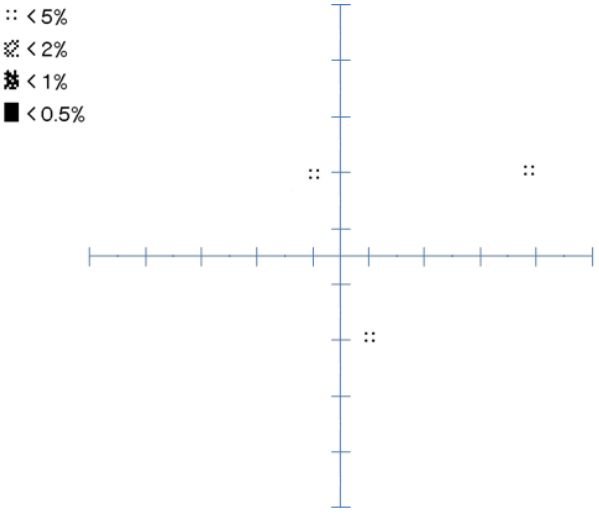


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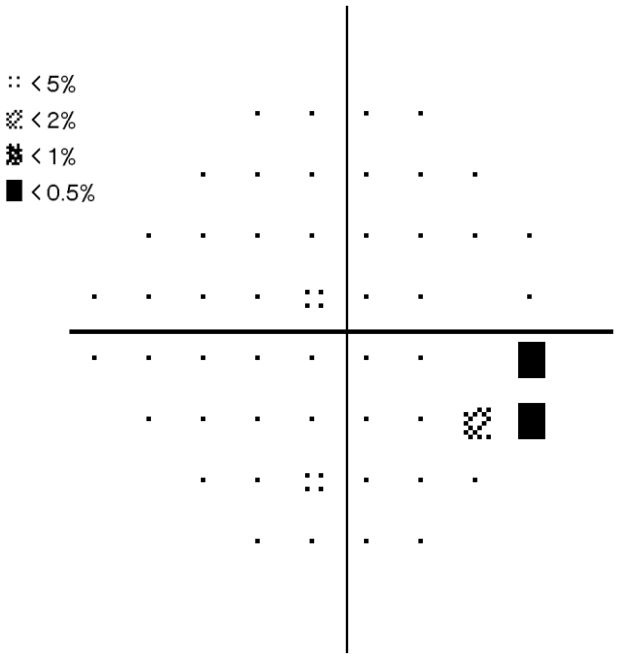


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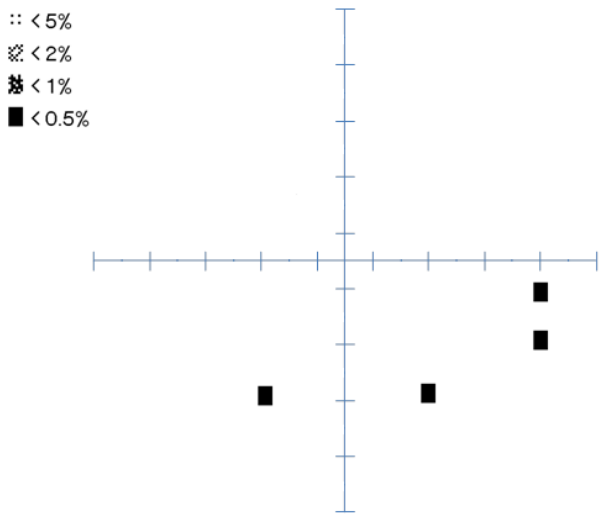


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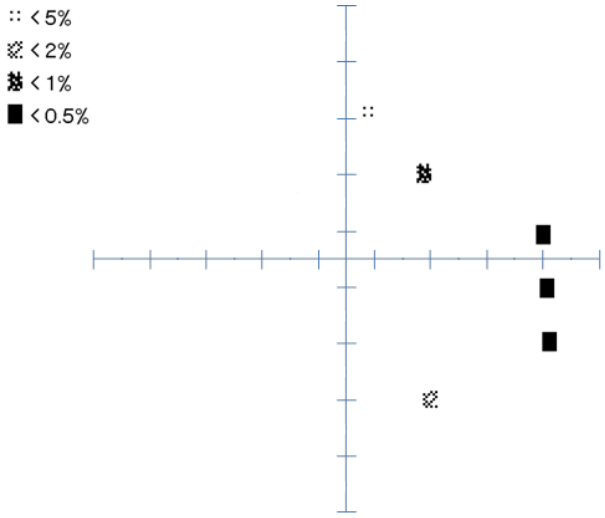


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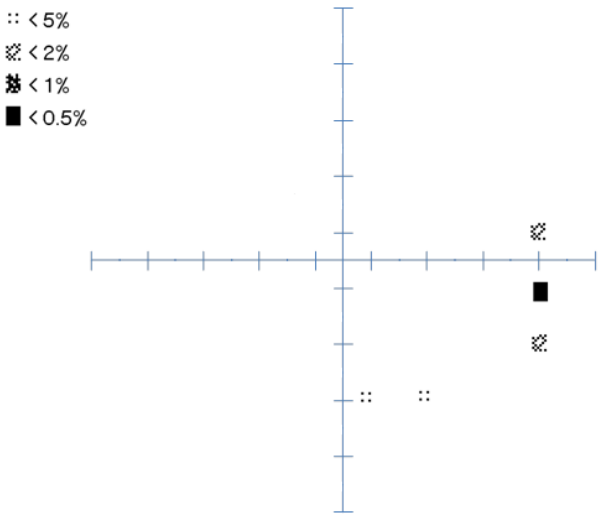


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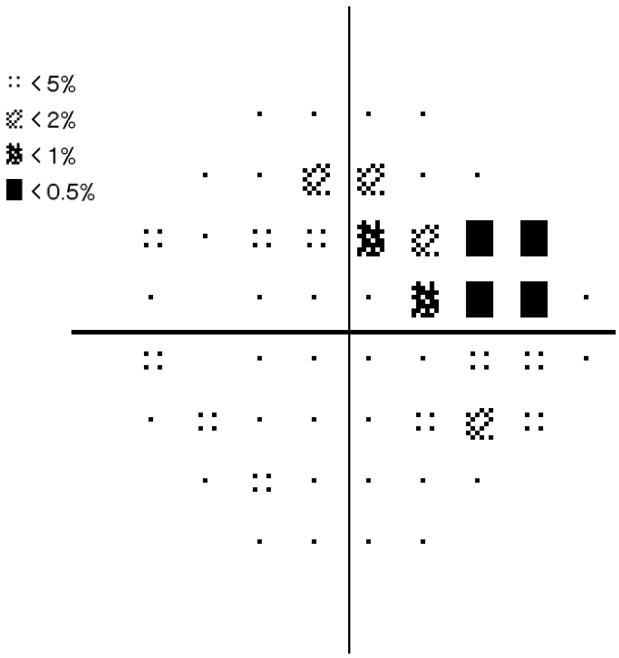


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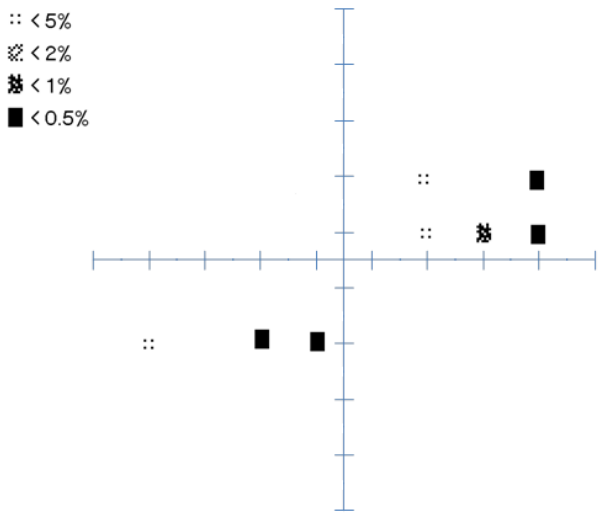


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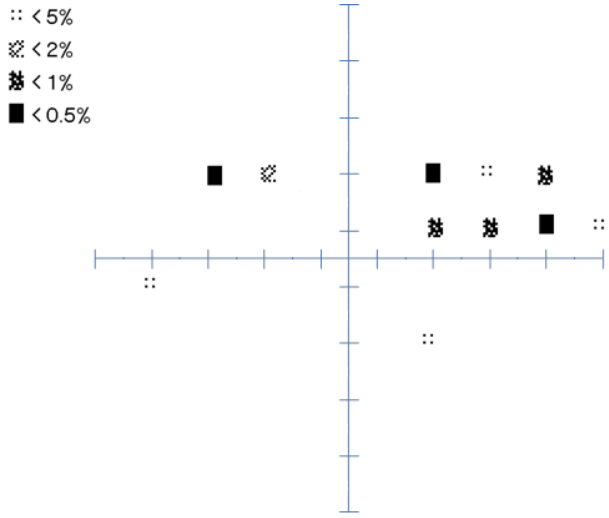


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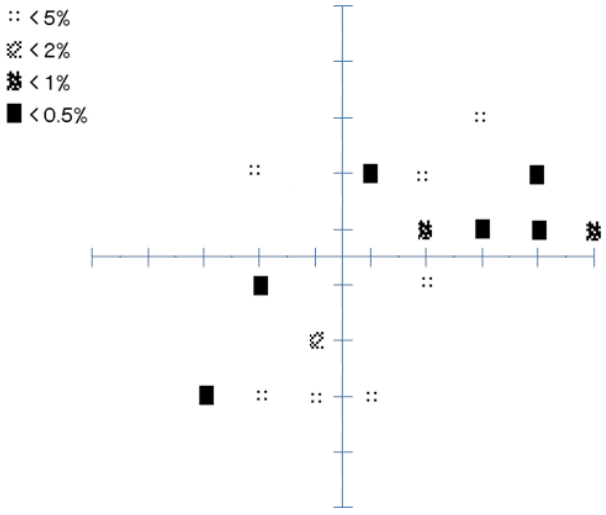


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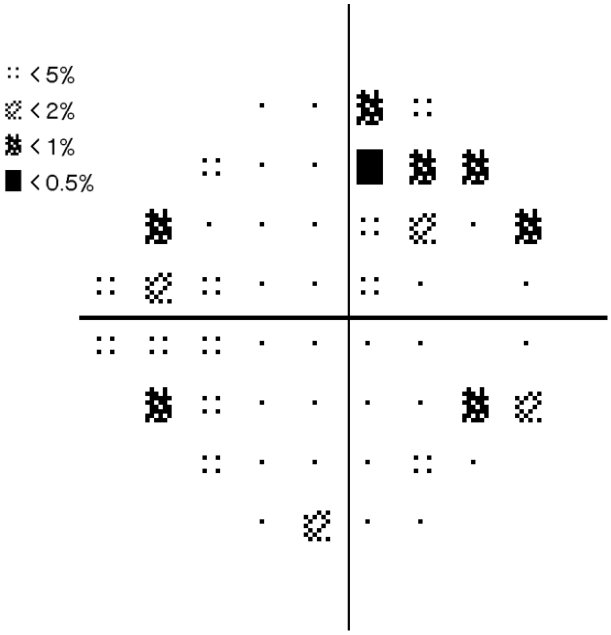


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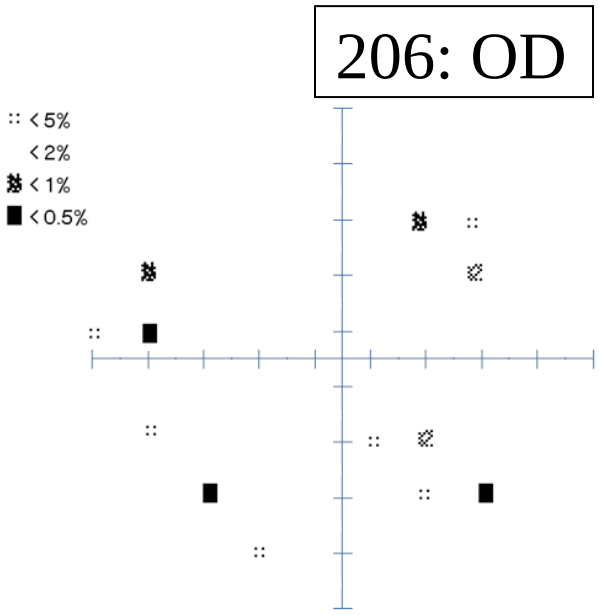


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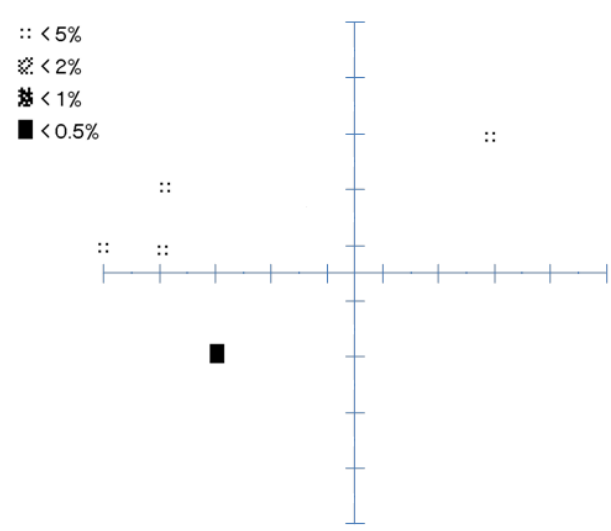


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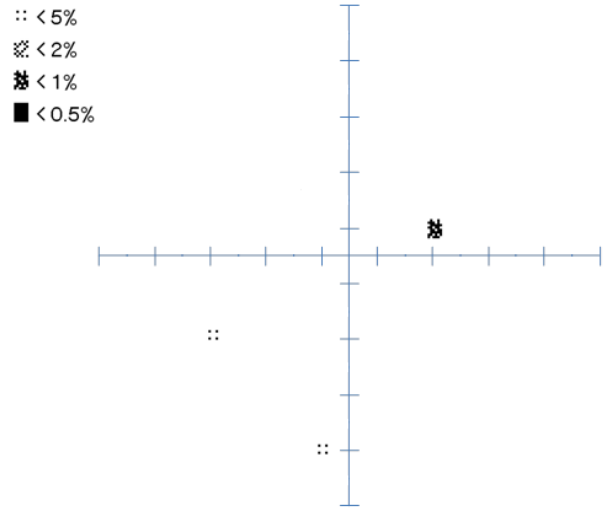


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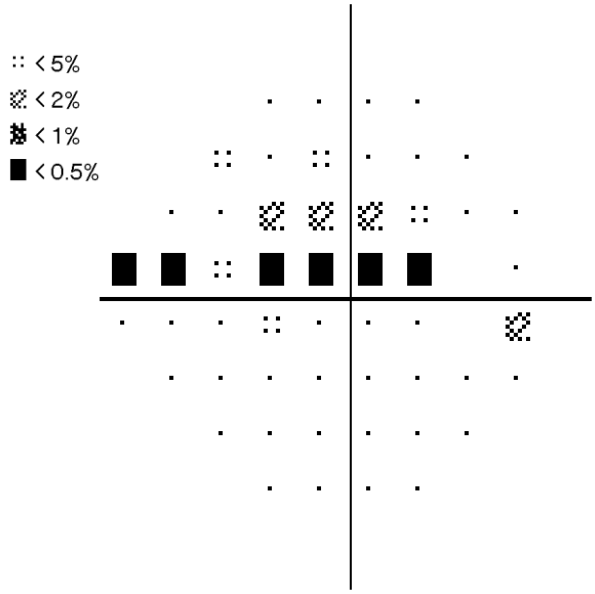


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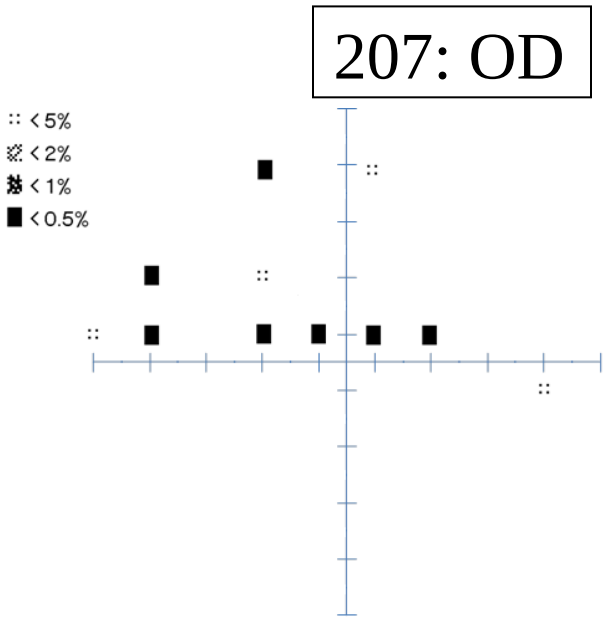


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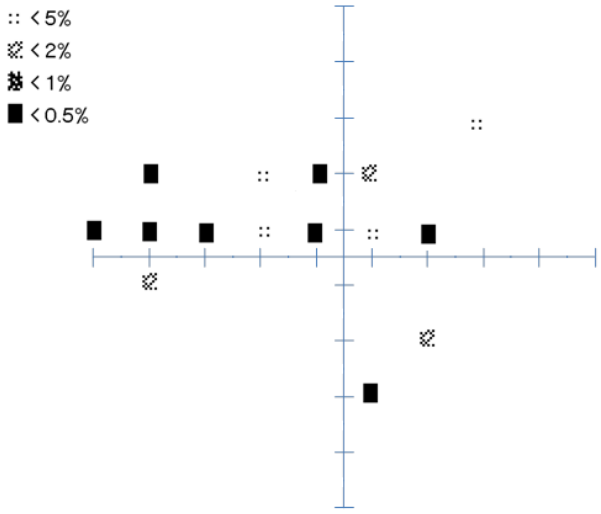


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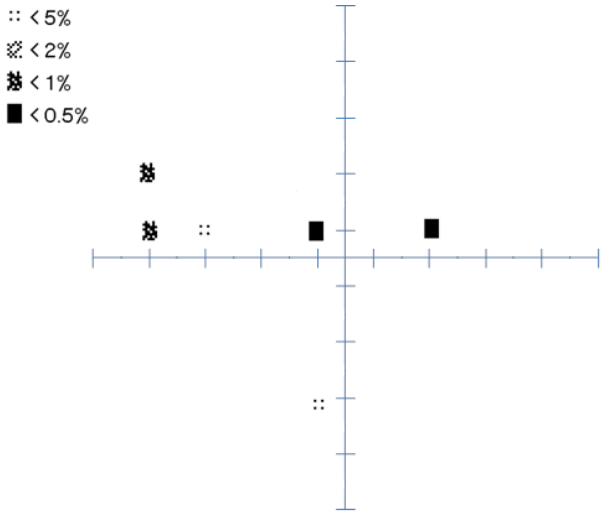


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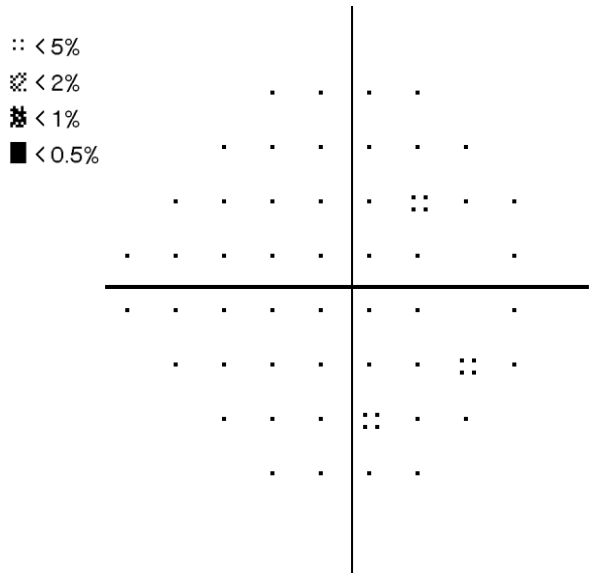


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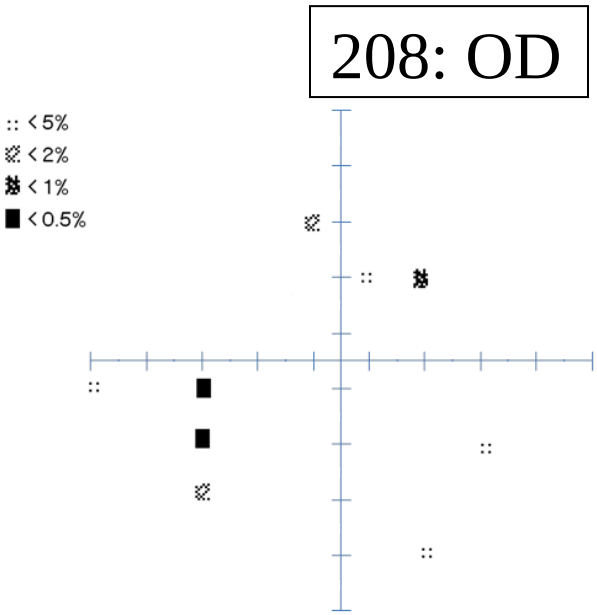


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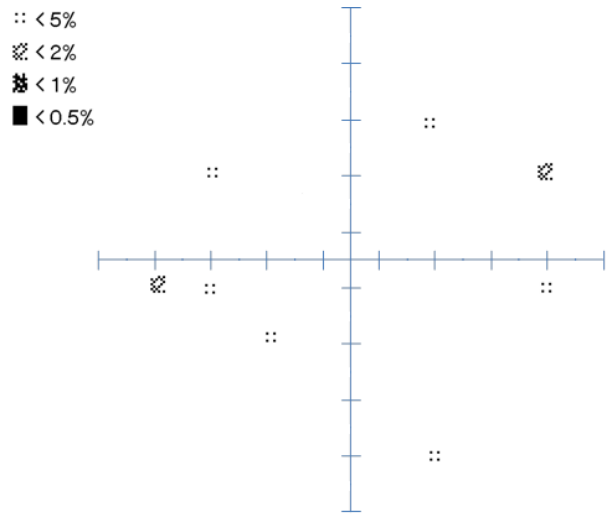


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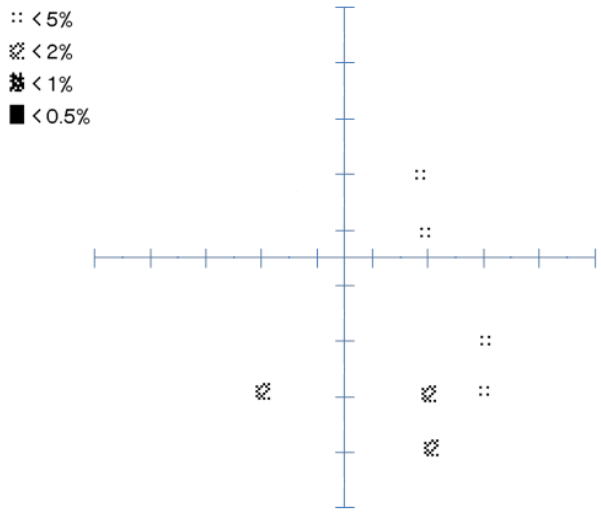


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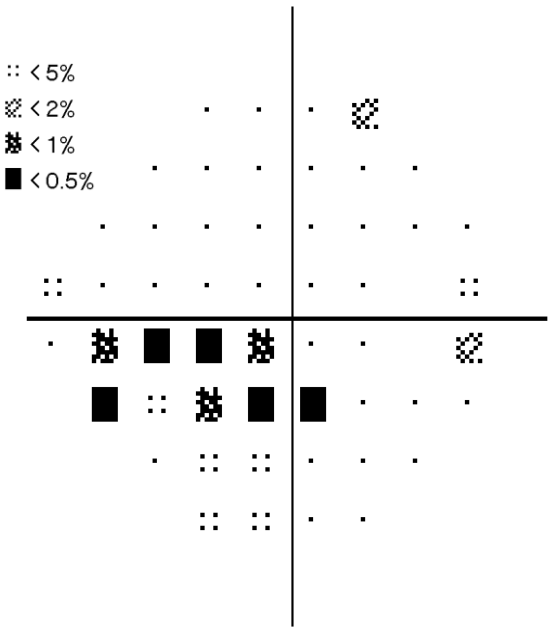


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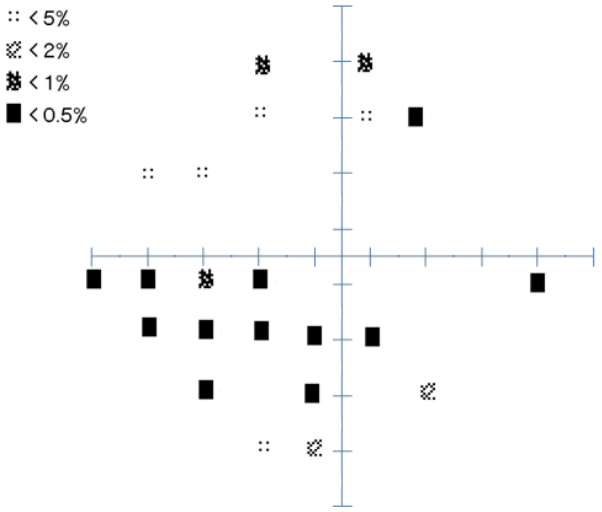


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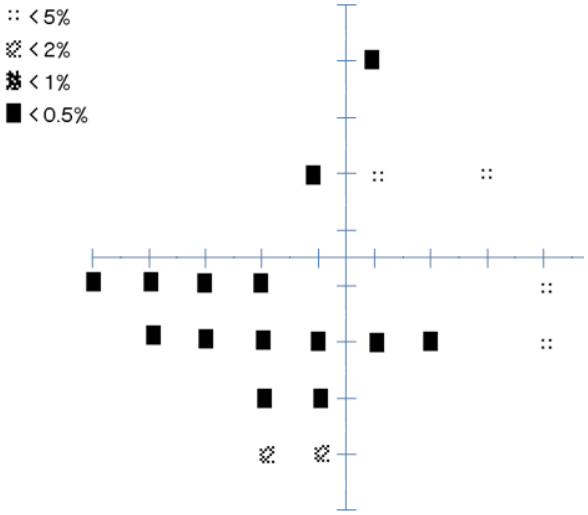


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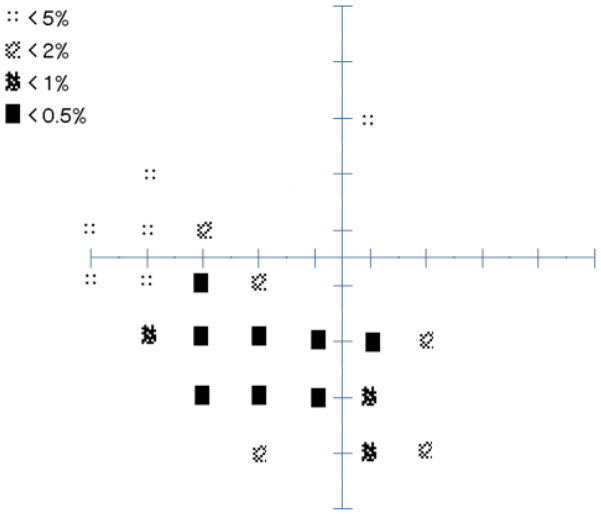


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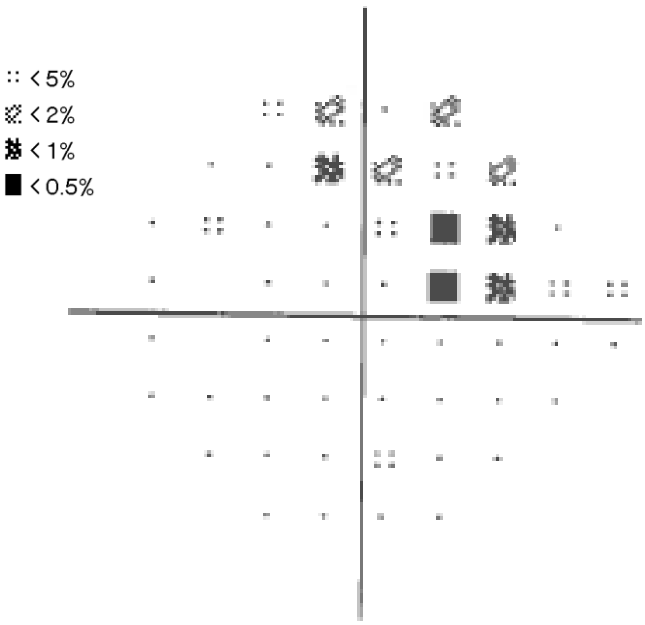


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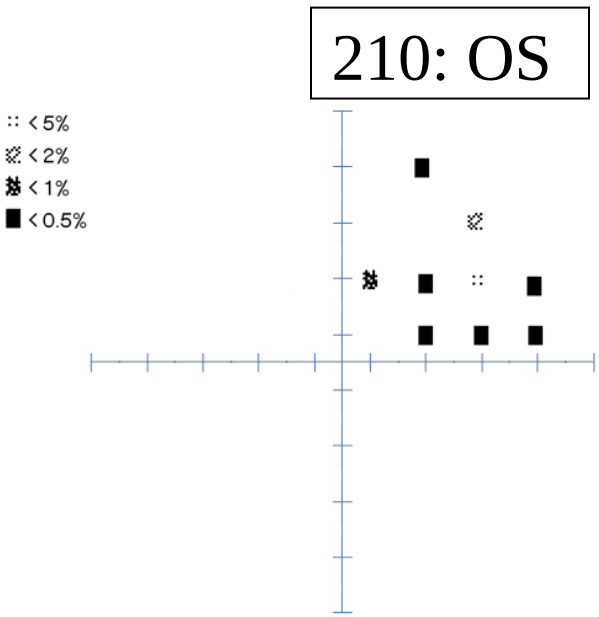


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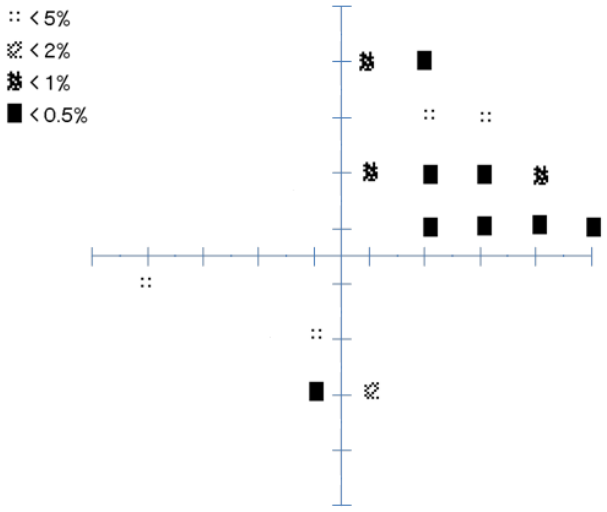


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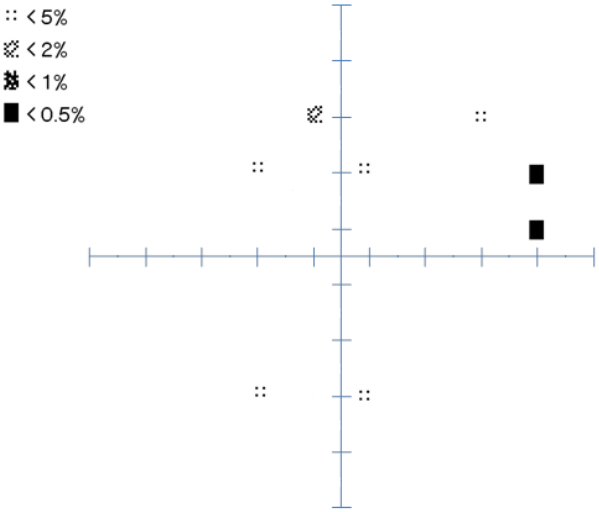


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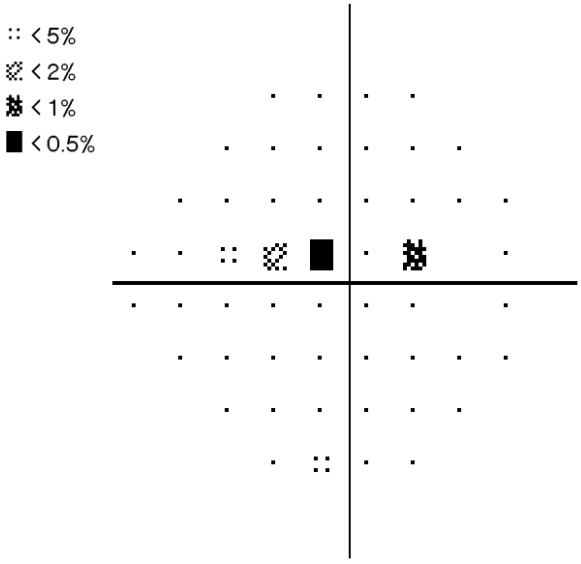


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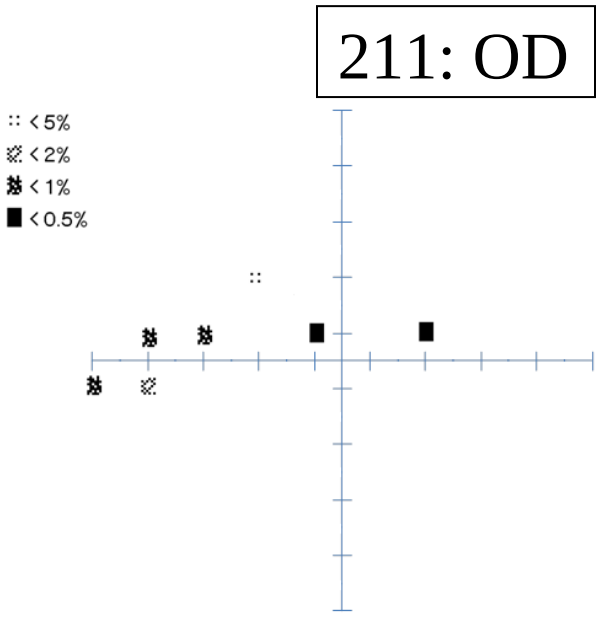


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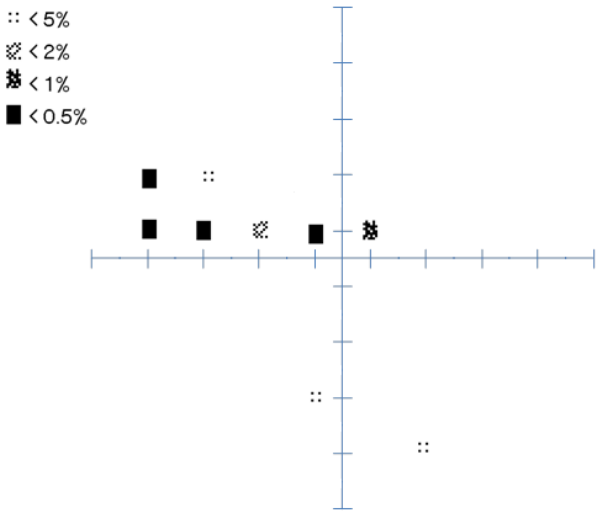


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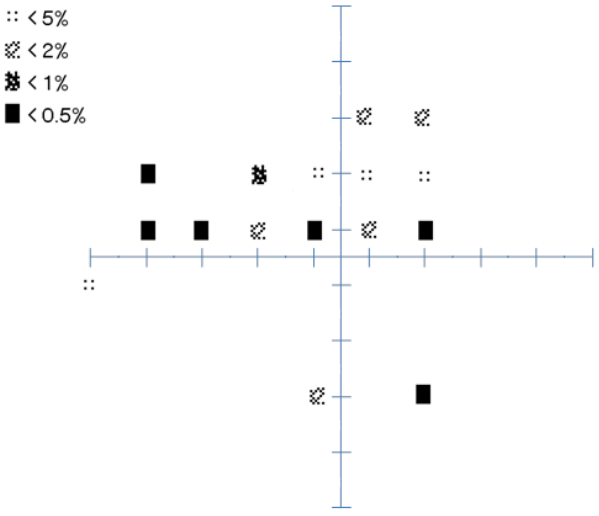


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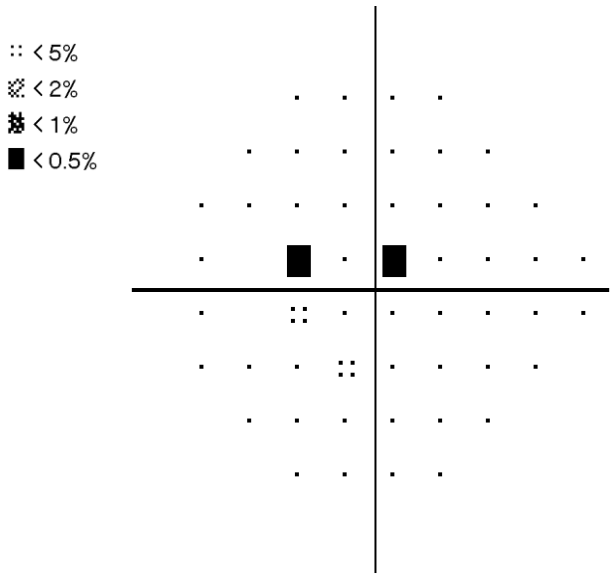


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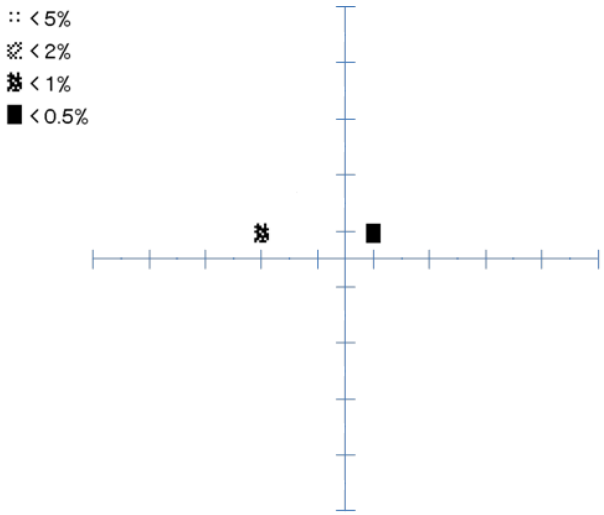


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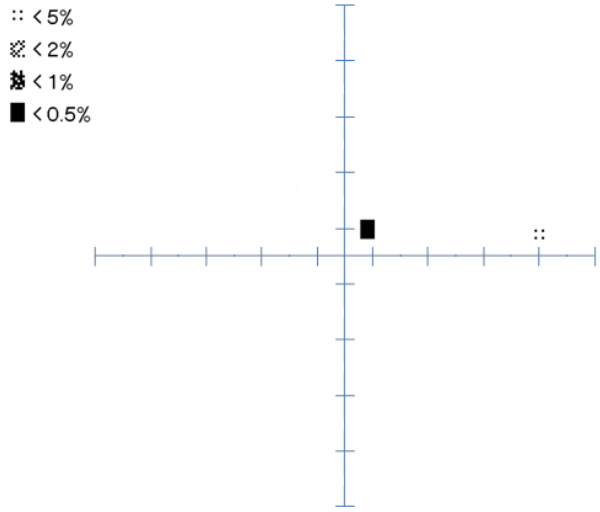


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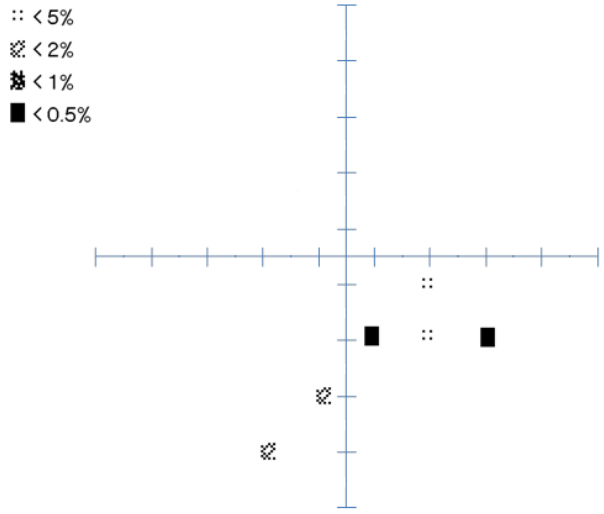


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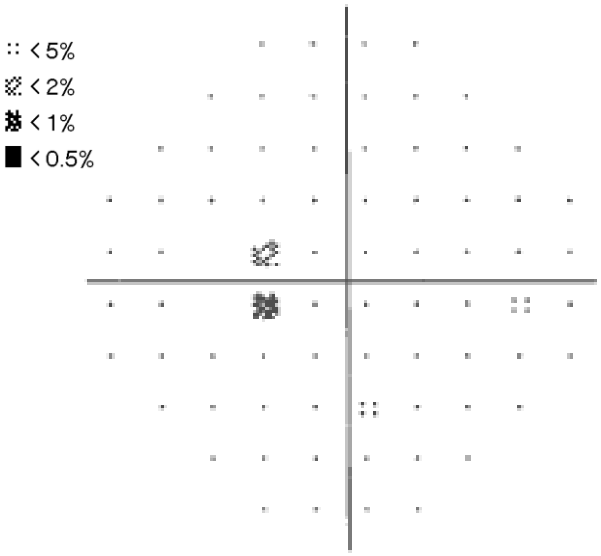


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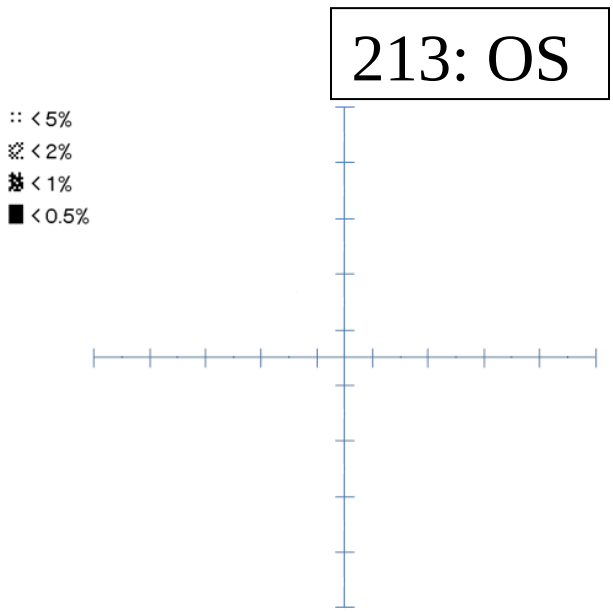


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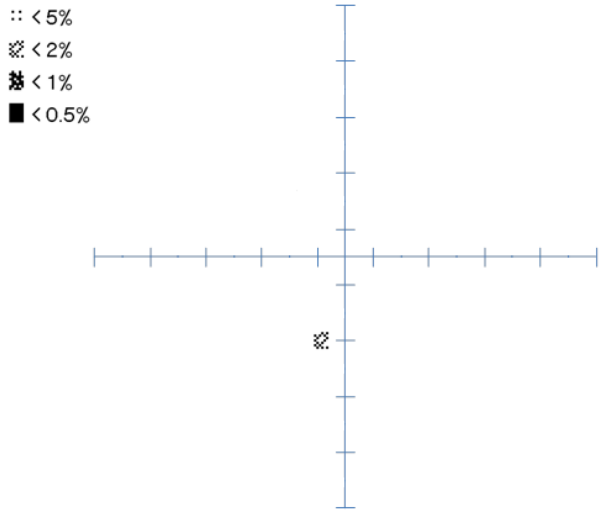


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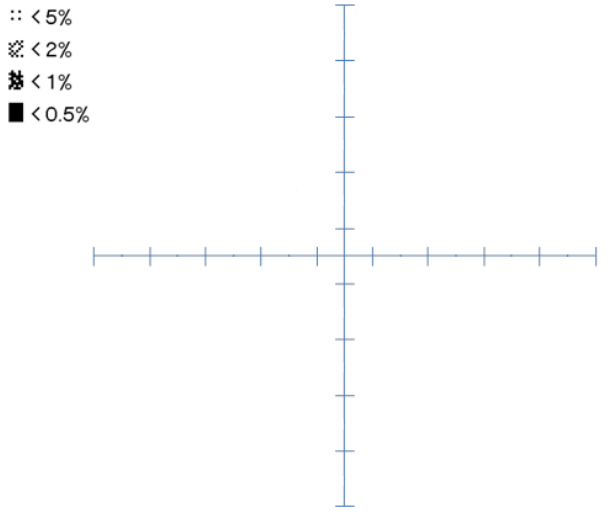


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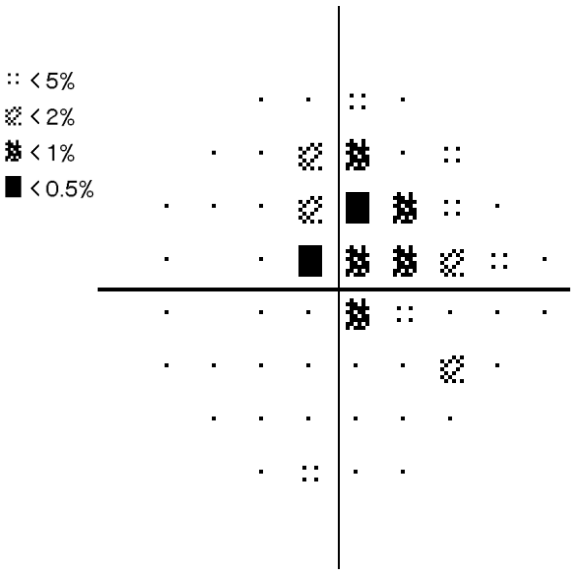


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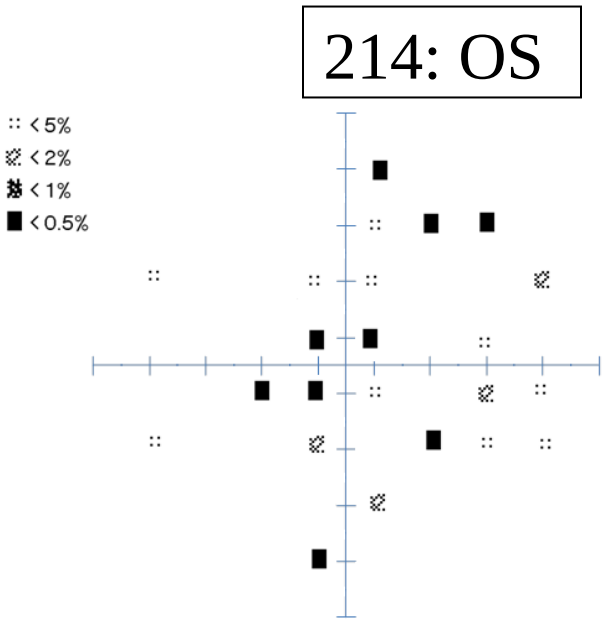


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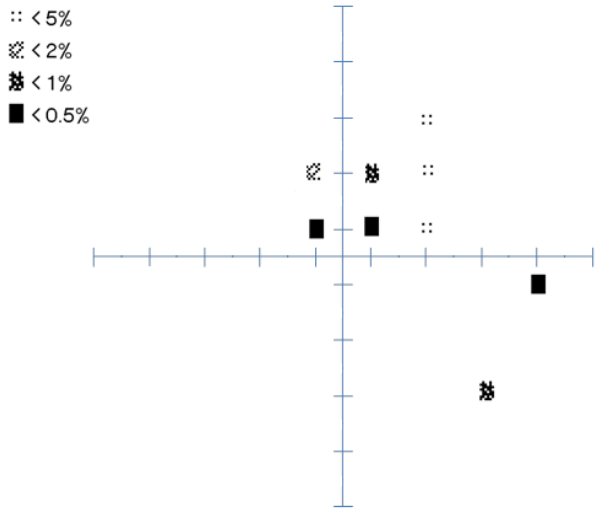


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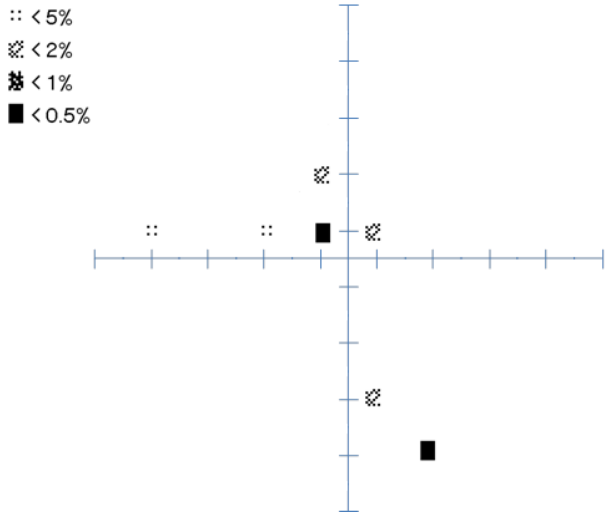


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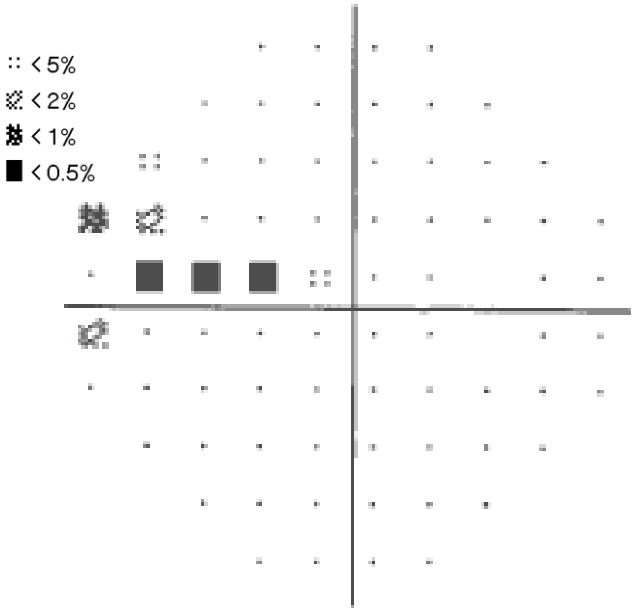


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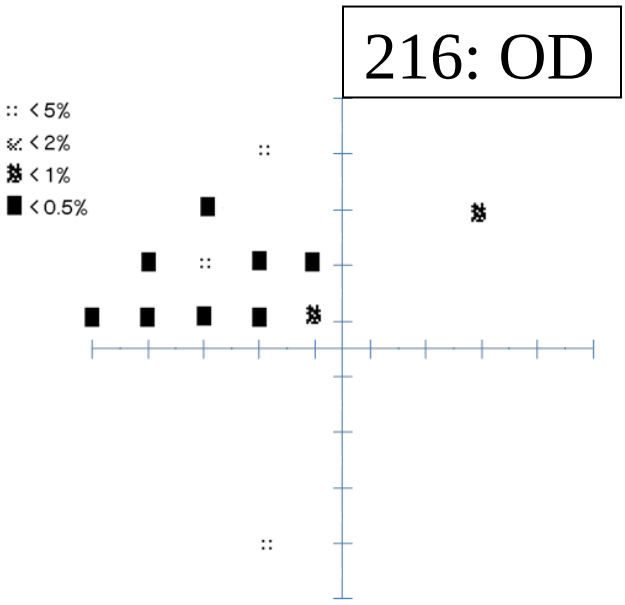


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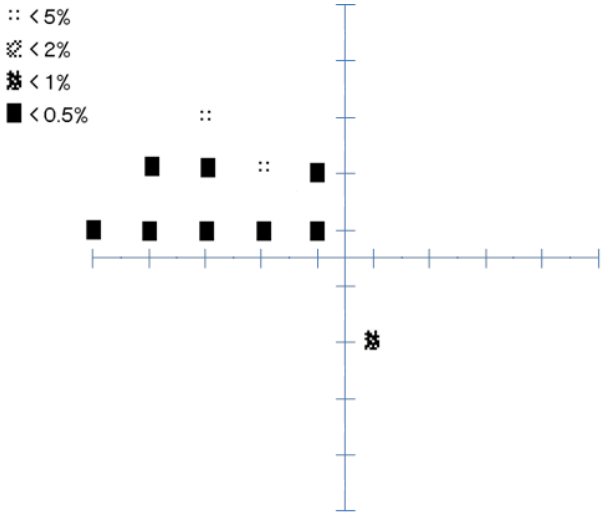


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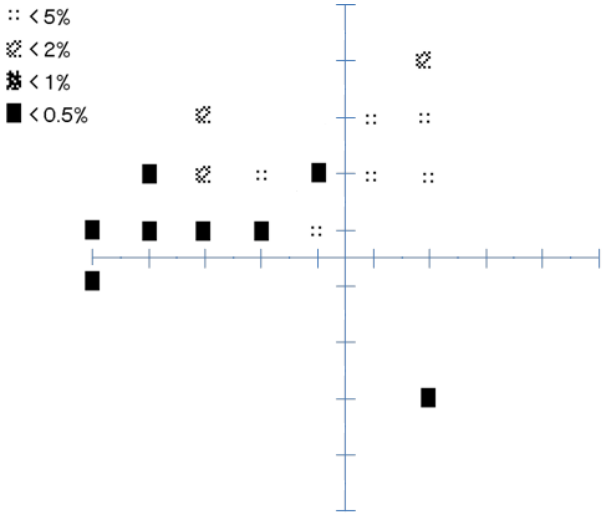


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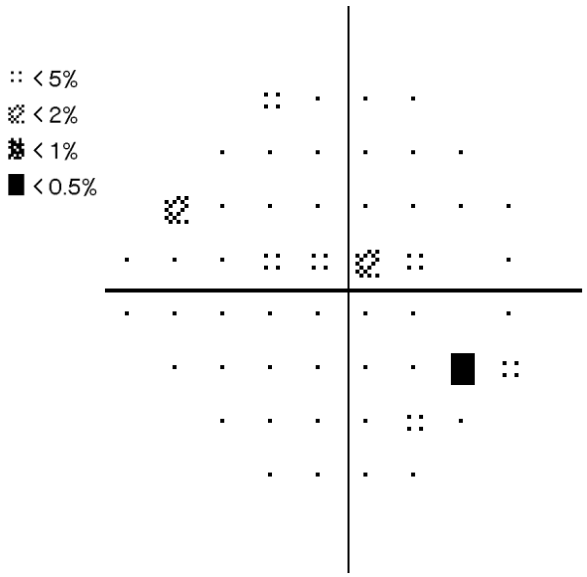


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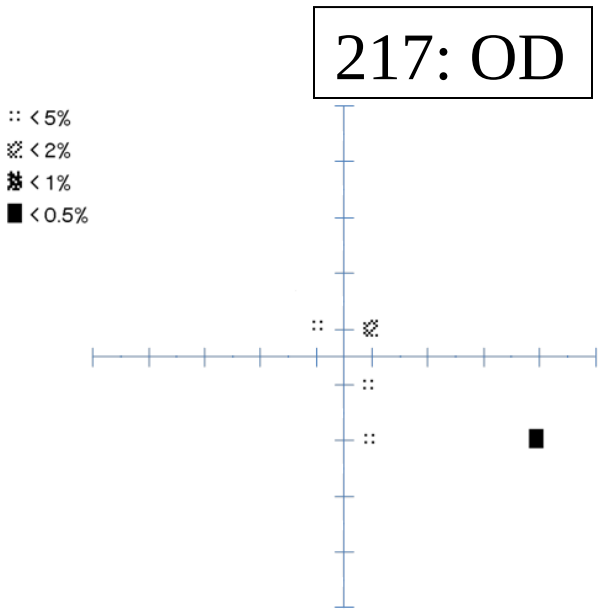


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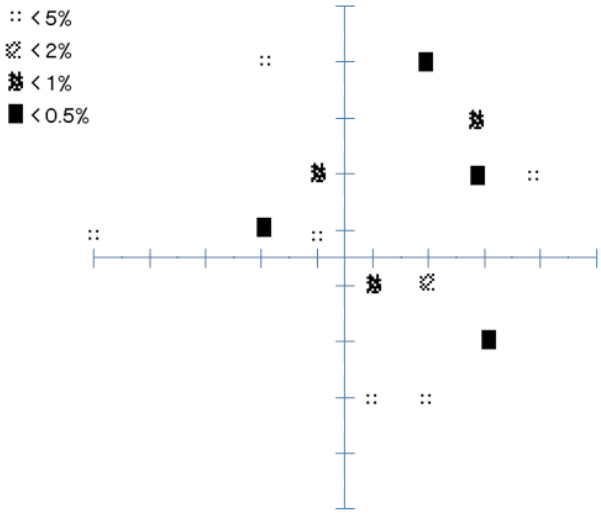


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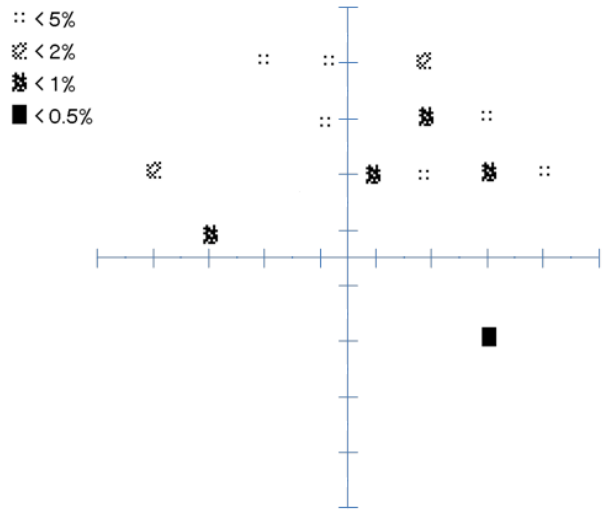


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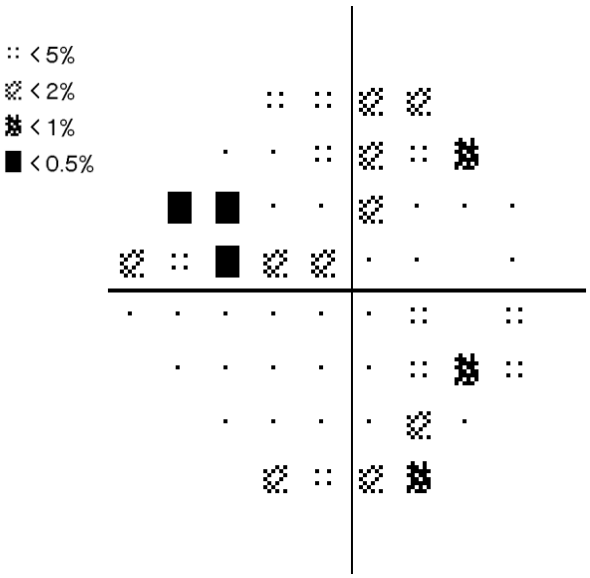


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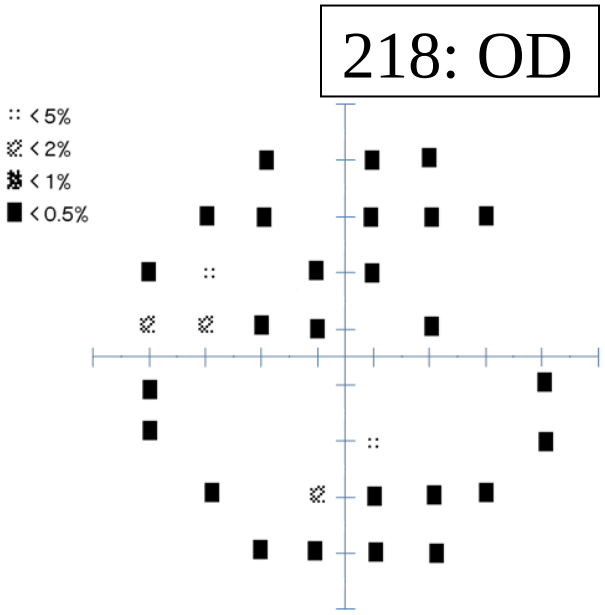


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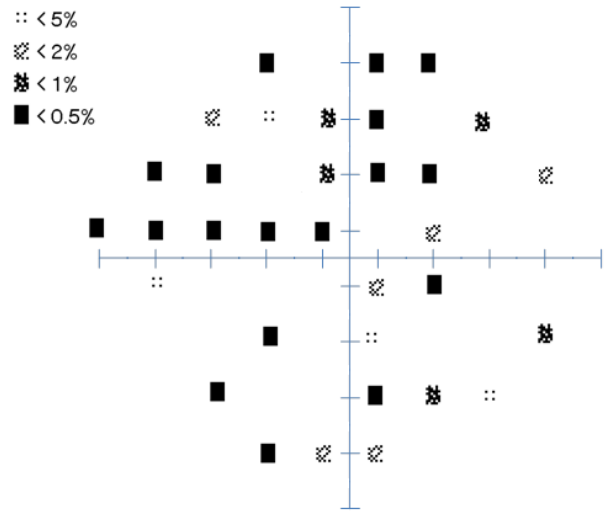


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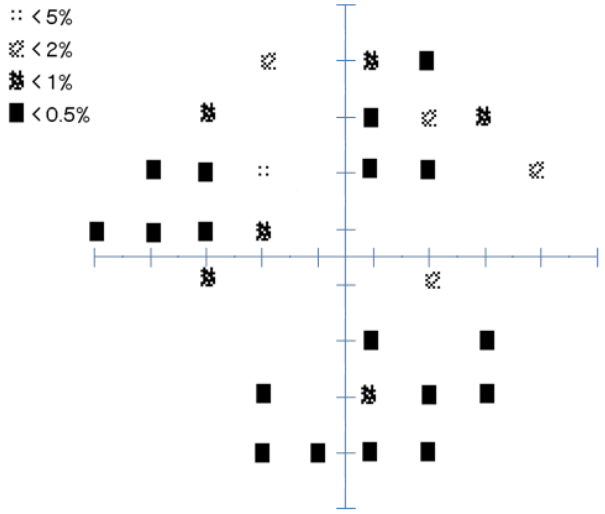


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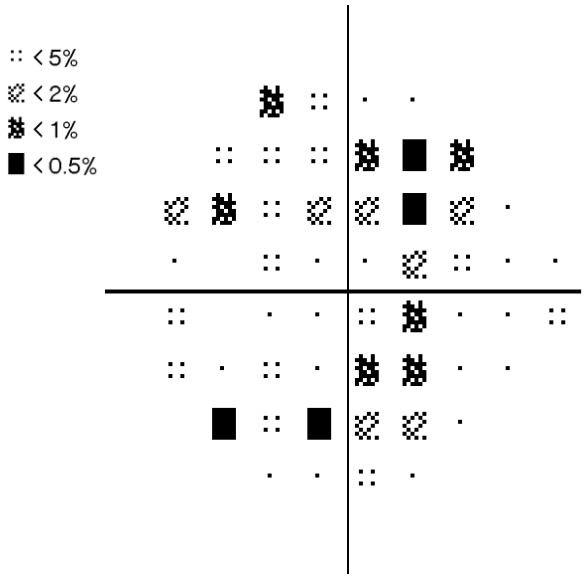


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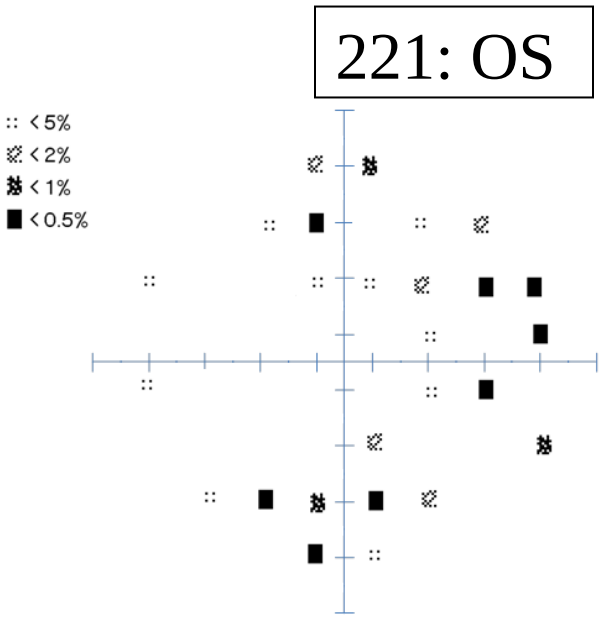


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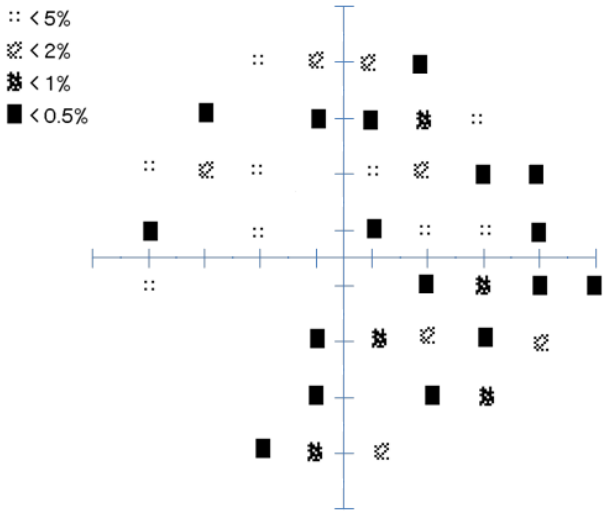


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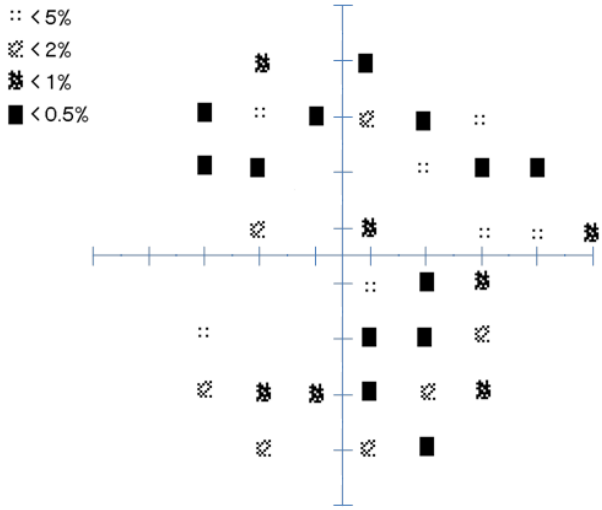


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# Bibliography

1. Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262-267.

2. Shields MB, Spaeth GL. The glaucomatous process and the evolving definition of glaucoma. *J Glaucoma*. 2012;21(3):141-143.

3. Harwerth RS, Vilupuru AS, Rangaswamy NV, Smith III EL. The relationship between nerve fiber layer and perimetry measurements. *Invest Ophthalmol Visual Sci*. 2007;48(2):763-773.

4. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. *Prog Retin Eye Res*. 2010;29(4):249-271.

5. Nilforushan N, Nassiri N, Moghimi S, et al. Structure-function relationships between spectral-domain OCT and standard achromatic perimetry. *Invest Ophthalmol Visual Sci*. 2012;53(6):2740-2748.

6. Leite MT, Zangwill LM, Weinreb RN, Rao HL, Alencar LM, Medeiros FA. Structure-function relationships using the cirrus spectral domain optical coherence tomograph and standard automated perimetry. *J Glaucoma*. 2012;21(1):49-54.

7. Leung CK-, Chong KK-, Chan W-, et al. Comparative study of retinal nerve fiber layer measurement by StratusOCT and GDx VCC, II: Structure/function regression analysis in glaucoma. *Invest Ophthalmol Visual Sci*. 2005;46(10):3702-3711.

8. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol*. 1991;109(1):77-83.

9. Matsumoto C, Shirato S, Haneda M, Yamashiro H, Saito M. Study of retinal nerve fiber layer thickness within normal hemivisual field in primary open-angle glaucoma and normal-tension glaucoma. *Jpn J Ophthalmol*. 2003;47(1):22-27.

10. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol*. 2005;123(4):464-470.

11. Reis ASC, Artes PH, Belliveau AC, et al. Rates of change in the visual field and optic disc in patients with distinct patterns of glaucomatous optic disc damage. *Ophthalmology*. 2012;119(2):294-303.

12. Anderson RS, McDowell DR, Ennis FA. Effect of localized defocus on detection thresholds for different sized targets in the fovea and periphery. *Acta Ophthalmol Scand*. 2001;79(1):60-63.

13. Bek T, Lund-Andersen H. The influence of stimulus size on perimetric detection of small scotomata. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 1989;227(6):531-534.

14. Wall M, Woodward KR, Doyle CK, Zamba G. The effective dynamic ranges of standard automated perimetry sizes III and V and motion and matrix perimetry. *Arch Ophthalmol*. 2010;128(5):570-576.

15. Lamparter J, Schulze A, Schuff A-, Berres M, Pfeiffer N, Hoffmann EM. Learning curve and fatigue effect of flicker defined form perimetry. *Am J Ophthalmol*. 2011;151(6):1057-1064.e1.

16. Engel Castro DP, Kawase J, Melo LAS. Learning effect of standard automated perimetry in healthy individuals. *Arq Bras Oftalmol*. 2008;71(4):523-528.

17. Wood JM, Wild JM, Bullimore MA, Gilmartin B. Factors affecting the normal perimetric profile derived by automated static threshold LED perimetry. I. pupil size. *Ophthalmic and Physiological Optics*. 1988;8(1):26-31.

18. Webster AR, Luff AJ, Canning CR, Elkington AR. The effect of pilocarpine on the glaucomatous visual field. *Br J Ophthalmol*. 1993;77(11):721-725.

19. Guthauser U, Flammer J. Quantifying visual field damage caused by cataract. *Am J Ophthalmol*. 1988;106(4):480-484.

20. Zborowski L, Kaleb-Landoy M, Luski M, Boaz M, Gaton D. Language of instruction and the effect on visual field results. *Harefuah*. 2008;147(11):855-857.

21. Gilpin LB, Stewart WC, Hunt HH, Broom CD. Threshold variability using different goldmann stimulus sizes. *Acta Ophthalmol*. 1990;68(6):674-676.

22. Fogagnolo P, Sangermani C, Oddone F, et al. Long-term perimetric fluctuation in patients with different stages of glaucoma. *Br J Ophthalmol*. 2011;95(2):189-193.

23. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophthalmol*. 1989;108(2):130-135.

24. Gardiner SK, Swanson WH, Goren D, Mansberger SL, Demirel S. Assessment of the reliability of standard automated perimetry in regions of glaucomatous damage. *Ophthalmology*. 2014.

25. Henson DB, Chaudry S, Artes PH, Faragher EB, Ansons A. Response variability in the visual field: Comparison of optic neuritis, glaucoma, ocular hypertension, and normal eyes. *Invest Ophthalmol Visual Sci*. 2000;41(2):417-421.

26. Wall M, Kutzko KE, Chauhan BC. Variability in patients with glaucomatous visual field damage is reduced using size V stimuli. *Invest Ophthalmol Visual Sci*. 1997;38(2):426-435.

27. Wall M, Brito CF, Woodward KR, Doyle CK, Kardon RH, Johnson CA. Total deviation probability plots for stimulus size V perimetry: A comparison with size III stimuli. *Arch Ophthalmol*. 2008;126(4):473-479.

28. Wall M, Woodward KR, Doyle CK, Artes PH. Repeatability of automated perimetry: A comparison between standard automated perimetry with stimulus size III and V, matrix, and motion perimetry. *Invest Ophthalmol Visual Sci*. 2009;50(2):974-979.

29. Wall M, Doyle CK, Zamba KD, Artes P, Johnson CA. The repeatability of mean defect with size III and size V standard automated perimetry. *Invest Ophthalmol Visual Sci*. 2013;54(2):1345-1351.

30. Wall M, Doyle CK, Eden T, Zamba KD, Johnson CA. Size threshold perimetry performs as well as conventional automated perimetry with stimulus sizes III, V, and VI for glaucomatous loss. *Invest Ophthalmol Visual Sci*. 2013;54(6):3975-3983.

31. Quaid PT, Flanagan JG. Defining the limits of flicker defined form: Effect of stimulus size, eccentricity and number of random dots. *Vision Res*. 2005;45(8):1075-1084.

32. Schiefer U, Pätzold J, Dannheim F. Conventional techniques of visual field examination. part I: Introduction - basics. *Ophthalmologe*. 2005;102(6):627-646.

33. Volbrecht VJ, Shrago EE, Schefrin BE, Werner JS. Spatial summation in human cone mechanisms from 0° to 20° in the superior retina. *Journal of the Optical Society of America A: Optics and Image Science, and Vision*. 2000;17(3):641-650.

34. Dobson V, Baldwin MB, Mohan KM, Delaney SM, Harvey EM. The influence of stimulus size on measured visual field extent in infants. *Optometry Vision Sci*. 2003;80(10):698-702.

35. Redmond T, Garway-Heath DF, Zlatkova MB, Anderson RS. Sensitivity loss in early glaucoma can be mapped to an enlargement of the area of complete spatial summation. *Invest Ophthalmol Visual Sci*. 2010;51(12):6540-6548.

36. Dannheim F, Drance SM. Studies of spatial summation of central retinal areas in normal people of all ages. *Canadian Journal of Ophthalmology*. 1971;6(4):311-319.

37. Harman A, Abrahams B, Moore S, Hoskins R. Neuronal density in the human retinal ganglion cell layer from 16-77 years. *Anat Rec*. 2000;260(2):124-131.

38. Malania M, Devinck F, Knoblauch K, Delahunt PB, Hardy JL, Werner JS. Senescent changes in photopic spatial summation. *Journal of Vision*. 2011;11(10):1-15.

39. Battista J, Badcock DR, McKendrick AM. Spatial summation properties for magnocellular and parvocellular pathways in glaucoma. *Invest Ophthalmol Visual Sci*. 2009;50(3):1221-1226.

40. Drance SM, Anderson DR. Physiological basis for perimetry. In: Drance SM, Anderson DR, eds. *Automatic Perimetry in Glaucoma. A Practical Guide.* Grune and Stratton, Inc.; 1985:18-,19,20,21.

41. Anderson DR. Basis of quantiative perimetry. In: Kist K, Rudoph P, eds. *Automated Static Perimetry.* Mosby Year Book; 1992:13.

42. Anderson DR. Basis of quantitative perimetry. In: Kist K, Rudolph P, eds. *Automated Static Perimetry.* Mosby Year Book; 1992:25.