

Review of the use of SWAP and FDT for the early detection of visual field loss.

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ABSTRACT

Background: To review the literature reporting SWAP and FDT for the early detection of visual field loss in glaucoma.

Methods: A review of literature published on Medline, Scopus and Web of Science between 1966 and present was undertaken with only articles in the English language reviewed.

Results: SWAP has high inter and intra subject variability. There is no uniform decision as to what criteria should be applied to define abnormal visual fields. In comparison with standard automated perimetry (SAP) there is controversy as to whether SWAP is reliable in detecting glaucomatous damage. As a screening tool FDT may have potential due to its short testing time and lower test-retest variability. There is a lack of definitive abnormality criteria to define visual field loss with FDT. First and second generation FDT have been found to be comparable to SWAP in terms of diagnostic sensitivity. There is a lack of studies comparing FDT to SAP with longitudinal follow up of visual fields which make it difficult to determine its reliability in identifying pre-perimetric glaucomatous damage.

Conclusion: There is a need for further longitudinal studies on both SWAP and FDT to determine fully their reliability in detecting early visual field loss in glaucoma before SAP.

Keywords: SWAP, FDT, Matrix, SAP, Glaucoma, Visual Field Evaluation

1. INTRODUCTION

Primary open angle glaucoma (POAG) is a chronic, potentially blinding condition caused by death of ganglion cells and their axons within the optic nerve due to increased pressure within the eye[1]. It affects approximately 3% of people over 65 in the UK and with average life expectancy in the UK rising, more people are now living with glaucoma even compared to the mid-90's[2,3]. The cost of treating glaucoma in the UK is more than £300 million per year. This includes both direct (medication, outpatient care, routine assessment and surgical procedures) and indirect treatment (cost of low vision services, loss of earnings resulting from vision loss)[4,5]. Glaucoma also affects quality of life with partial sight or registered severely sight impaired being ultimate possibilities. One of the determinants for a poor visual prognosis is signs of glaucomatous field damage upon presentation to the clinician. This means vision and visual field could be potentially saved if damage could be reliably detected before current visual field analysis is able to[6,7]. Glaucoma diagnosis and progression are determined by three factors; intraocular pressure (IOP) changes, optic disc examination and visual field evaluation. There are a number of methods which can be used to evaluate the visual field including standard automated threshold perimetry, frequency doubling

36 technology, critical flicker frequency, short wavelength automated perimetry, high pass
37 resolution perimetry and motion automated perimetry amongst others.

38 Within the visual pathway there are a number of sub-pathways that subserve different
39 aspects of vision and whose physiological properties are distinct. The M (magnocellular)
40 pathway consists of larger retinal ganglion cells that are mainly linked with visual perception
41 and respond predominantly to motion and coarse outlines. They are regarded as insensitive
42 to colour stimuli in balanced luminance conditions, respond to high contrast sensitivity and
43 resolve higher temporal and lower spatial frequencies[8,9]. The K (koniocellular) pathway
44 consists of smaller, sparse retinal ganglion cells that are sensitive to short wavelengths
45 (S/blue cones)[8-10]. The spatial and temporal resolutions of the K pathway overlap with the
46 M and P pathways[11]. The P (parvocellular) pathway consists of small retinal ganglion cells
47 that are sensitive to colour (particularly red/green), respond predominantly to fine details and
48 to lower contrast sensitivity. They resolve lower temporal and higher spatial frequencies[8,9].
49 It is possible to isolate responses from the M, P and K pathways by using different testing
50 stimuli. Strategies to isolate the P and K pathways include the use of coloured, high contrast,
51 small stimuli whereas strategies to isolate the M pathway include the use of stimuli that are
52 colour neutral, have high temporal and low spatial frequencies such as large, fast motion
53 reversal, low contrast targets.

54 It is known that in early glaucoma, larger ganglion cells within the optic nerve are damaged.
55 First the blue-yellow ganglion cells (part of the koniocellular pathway) which are larger than
56 red-green ganglion cells are damaged leading to dyschromatopsia[12]. This effect has been
57 exploited in testing for early glaucoma damage by using short wavelength automated
58 perimetry (SWAP). SWAP is used with blue points (wavelength 440nm) with a narrow band
59 presented for 200msec on a yellow background (100cd/m^2) to try and detect early colour
60 vision loss[3]. Studies have shown that SWAP perimetry can detect glaucomatous damage
61 3-5 years before conventional white on white perimetry[13-15]. With current standard white
62 on white perimetry around 30-50% of ganglion cells have been destroyed before
63 detection[16].

64 Furthermore, the M pathway can be isolated when assessing for early glaucoma. Frequency
65 doubling technology (FDT) was first described by Kelly over 45 years ago. It is based on the
66 fact that when an achromatic sinusoidal grating of low spatial frequency undergoes flickering
67 at high temporal frequency the apparent spatial frequency of the grating appears to
68 double[17]. The response to this is thought to be mediated by M_y -cells, which are sensitive to
69 low contrast and motion stimulus. M_y cells are again larger than other retinal ganglion cells
70 (part of the magnocellular pathway) and are therefore more prone to damage in early
71 glaucoma[18]. This forms the rationale for using FDT as a potential visual field screening
72 method for early glaucoma detection.

73 There is an alternative theory as to why SWAP and FDT may be able to detect early
74 glaucomatous damage: as a result of the reduction in the redundancy in the visual
75 system[19]. The function-specific tests isolate a subset of ganglion cells which may lead to
76 an increased sensitivity to early ganglion cell loss.

77
78 There has been conflicting evidence regarding the use of SWAP and FDT for early detection
79 of visual field loss. The aim of this review is to evaluate the literature in respect to whether
80 FDT and SWAP perimetry can reliably detect glaucomatous visual field changes before
81 Humphrey SAP.

82

2. METHODOLOGY

The SCOPUS, Web of Science, PubMed and Medline databases were searched for the following terms: SWAP and glaucoma, Short Wavelength Automated Perimetry and glaucoma, SWAP and ocular hypertension and Short Wavelength Automated Perimetry and ocular hypertension, SWAP and open angle glaucoma, SWAP and closed angle glaucoma, Frequency Doubling Technology and glaucoma, FDT and ocular hypertension, Frequency Doubling Technology and open angle glaucoma, Frequency Doubling Technology and angle closure glaucoma, Frequency Doubling Technology and Short Wavelength Automated Perimetry, Frequency Doubling Technology and screening, Matrix FDT and ocular hypertension, Matrix FDT and glaucoma and Matrix FDT and closed angle glaucoma.

We included international articles but only those written in English were reviewed due to lack of access to translation facilities. The years included were from the year 1966 to 2013. In this review only studies reporting the use of SWAP and/or FDT for early visual field loss in glaucoma detection are considered.

We found 2917 articles from our search, accessed 112 full articles which were assessed as relevant to the review topic and evaluated 79 articles for this review article.

3. RESULTS AND DISCUSSION

3.1 Short Wavelength Automated Perimetry (SWAP)

SWAP is a type of visual field assessment which is based on the principle that larger ganglion cells within the retina are selectively damaged during early glaucoma. Ten per cent of these larger ganglion cells belong to the blue-yellow pathway: part of the koniocellular pathway[12]. The earlier death of this ganglion cell population has also been confirmed by histological evidence[20-22]. The blue-yellow conditions of SWAP isolate the S cone system (short wavelength cones), reduce the participation of other cone systems (red – long wavelength and green – medium wavelength) and saturate the rods activity through the adaptation to yellow light[23,24]. This phenomenon has been reported to be of use to predict glaucomatous visual field damage up to 4 years before it is detected on standard achromatic perimetry[13,14].

SWAP can be performed on the Humphrey Visual Field Analyser (HVF: Carl Zeiss Meditec Inc., Dublin, CA, USA) and the Octopus perimeter (Haag Streit Int., USA). A Goldman size V target (1.74° diameter) is used with a blue filter placed over the source of light allowing only light with a peak transmission of 440nm through. The white background light is replaced by yellow light illuminated at 100cdm² in the perimeter bowl. The targets are presented for 200msec in all test locations. The test is performed within the central 30 degrees of the visual field.

SWAP has not been introduced routinely into clinical practice due to a number of factors: clinicians are not united on a definition of abnormality criteria[25], the effect of the ageing lens on results[26], lengthy test time[24], patient fatigue and patient's dislike of the test[27] and the large intra and inter-subject variability even with normal subjects[28] which make it difficult to define an abnormal field. Some of the factors causing a barrier to its use in practice will be addressed in more detail: i.e. test time by means of test choice and abnormality criteria.

3.1.1 Test (Algorithm) Choice

129 The lengthy test time for SWAP is an important factor and, as stated above, is one of the
130 reasons why SWAP is not routinely used in clinical practice. One way in which test time for
131 SWAP could be reduced is to consider the choice of algorithm. There are a number of test
132 programmes (algorithms) that can be used around which there is debate as to which should
133 be used. Current versions available for SWAP include a full-threshold option whereby a
134 staircase method is used to plot sensitivity at specific test locations[29]. A SITA-FAST
135 (Swedish Interactive Threshold Algorithm) version of the SWAP algorithm was developed
136 which reduced testing time by up to 70% (11 minutes with full threshold and just over three
137 minutes with SITA-SWAP) with no apparent reduction in sensitivity of specificity[30]. It is also
138 reported that the SITA-SWAP algorithm partially reduces the issue of the large inter-subject
139 variability by approximately 14%[29-31].

140 **3.1.2 Abnormality Criteria**

141 The statistical properties of SWAP have been examined extensively, firstly by Wild *et al* [26]
142 who tried to establish a normal database containing probability levels and analysis
143 synonymous to that for SAP. An increased between level variability was found between
144 subjects compared to SAP with the variability increasing with target eccentricity and
145 increasing age. This is relevant as the risk of developing glaucoma increases with age[32].
146 The between subject variation is also important to note when looking at probability maps to
147 define an abnormal field. To use the same level of depression required for SAP would be
148 unwise as this will lead to a large number of false positive results. This adds evidence for the
149 need to design bespoke statistical analyses rather than a cross-over with SAP.

150 This view was also supported by Kwon *et al.* [33] showing a similar amount of variation upon
151 repeated testing. Both studies had a similar number of participants making their results
152 comparable, however, neither provided an indication of what may be an appropriate criterion
153 for what 'normal' may be.

154 Polo and associates[25,34,35] aimed to suggest and refine abnormality criteria for SWAP by
155 addressing the sensitivity and specificity at different probability levels. They suggested that
156 using cluster point criteria (four points clustered at the $P < 5\%$ level or three points clustered
157 lower than $P < 1\%$), rather than using global indices, provide the best sensitivity and
158 specificity. A criticism of the classification of the criteria they used to define glaucomatous
159 damage was inclusion of changes in the retinal nerve fibre layer as opposed to the gold
160 standard optic nerve head assessment (optic nerve images taken by photography). NICE
161 guidelines suggest optic nerve changes are more indicative of glaucomatous damage than
162 retinal nerve fibre layer assessment as the latter damage is not always present yet the
163 patient can have other characteristics of glaucoma including raised IOP, optic disc cupping
164 and visual field loss[36].

165 This view is also supported by Johnson *et al* [37] who suggested four abnormal points at the
166 $P < 5\%$ level are indicative of glaucomatous visual field loss. Johnson and associates [37]
167 used their own controls in their study to define a normative database rather than the
168 parameters provided in the perimeter. However, they did test the validity of their controls
169 before comparing these with their 'abnormal' group and their normative dataset is large and
170 almost double that of Polo and colleagues[25,34,35] Although the normative database is
171 large the visual fields were only performed once on the control subjects who had no prior
172 knowledge of the test whereas the abnormal group had at least four years' experience on
173 both SAP and SWAP. It has been shown that there is a significant learning effect for both
174 SWAP and SAP so it is possible the control subjects performed worse on the perimetry tests
175 which made them more comparable to the abnormal patients showing signs of reduced
176 sensitivity[38-40].

The work by Polo [25,34,35] and Johnson [37] is valuable and upon repeated testing Reus *et al.* [41] found that Polo's [25] criteria for abnormality on SWAP seemed to obtain more positive results compared with Johnson's criteria[37]. There was still a large variation in the amount of positives obtained depending on which criteria were used. Reus *et al.* [41] allowed for the learning effect which appears to improve specificity[42]. No indication was provided regarding the end point of the study and subjects were not followed up to determine if SAP defects persisted or developed.

There is little research to date that has specifically addressed the definition of an abnormality criteria set for SWAP. Many studies use their own normative data and their own diagnostic criteria as to what constitutes a defect. This introduces uncertainty as to whether SWAP can be a clinically useful tool. Further work is required to create a "gold standard" diagnostic criterion for SWAP in order to make direct comparisons between studies. A summary of the studies attempting to define a abnormality criteria set is shown in Table 1.

3.1.3 SWAP and SAP

The initial SWAP studies followed ocular hypertensive and early glaucoma patients for five years to determine whether SWAP was able to predict those patients who would go on to develop glaucomatous visual field damage. Johnson *et al.* [13,14] and Sample *et al.* [43] showed promise in the use of blue-on-yellow perimetry to detect visual field loss before standard white on white perimetry but with a number of limitations. Explicit criteria for a deficit on white on white perimetry was used (<5% probability level for mean deviation (MD) or pattern standard deviation (PSD) or more than three points clustered at the <5% level).

Table 1. Summary of studies attempting to define abnormality criteria for SWAP.

Study	Sample Size	Control Group Used	Suggested Abnormality Criteria	Follow up Period
Kwon <i>et al.</i> 1998 [33]	31 eyes	33 eyes	None suggested	8 weeks
Polo <i>et al.</i> 2002 [25]	95 eyes	128 eyes	Four clustered points at P<5% level or three clustered points at P<1% level	3 years
Johnson <i>et al.</i> 2002 [37]	479 eyes	348 eyes	Four clustered points at P<5% level	4 years
Reus <i>et al.</i> 2005 [41]	744 eyes	None used	Four clustered points at P<5% level	6 months up to 1 year
Van der Shoot <i>et al.</i> 2009 [45]	416 eyes	None used	None suggested and compared directly with SAP criteria of at least 3 points at P<5% with at least two at P<1% level or corrected PSD <5%	7 to 10 years

199

200 No such criterion was implemented for blue-on-yellow as to what actually constituted a
 201 defect. It was evident there was a lot of variance even between tests with defects presenting
 202 and disappearing upon repeated testing. Their initial test conditions did factor in absorption
 203 of yellow light which is important as the ocular media can act as a neutral density filter
 204 particularly in the presence of cataract [44]. Their sample size for which they base their
 205 results on is relatively small for the amount of people potentially available with ocular
 206 hypertension. One issue with the results obtained in the early studies was the reporting of
 207 defects in terms of total deviations rather than pattern deviation which is important. Total
 208 deviation provides an indication of the depression of the hill of vision whereas pattern
 209 deviation gives an indication of the abnormality of the shape of the field. They did however
 210 age match their patients but this was only against a maximum of 22 subjects. Considering
 211 the variability that SWAP produces this may not be an entirely appropriate approximation of
 212 glaucomatous field loss. The results from the papers published by Johnson and colleagues
 213 [14,15] and Sample and colleagues [43] are what have driven subsequent studies.

214 Interestingly the subjects recruited by Polo and colleagues [34] to establish their abnormality
 215 criteria were recalled three years later [35] to determine how many had developed a defect
 216 on SAP. There was a high percentage who were deemed to have a SWAP defect and did
 217 not go onto develop glaucomatous damage after three years indicating the specificity of the
 218 test was not high and in the region of 30%.

219 There have been contradictions to the supporting evidence for SWAP. Van der Shoot et al
 220 [45] state SWAP is less sensitive than SAP to predict conversion to glaucoma. However, in
 221 their study, no correction criteria were provided for cataract which is known to decrease the
 222 mean sensitivity of SWAP by absorption of the short wavelength light in the lens. This is
 223 important considering that the age range used in their study would include those starting to
 224 develop cataract [26]. The conversion to glaucoma, which was the end point of the study,
 225 was based purely on visual field analysis. No anatomical correlation (e.g. optic nerve head
 226 cupping) was sought that matched with the visual field defect.

227 Liu *et al.* [46] also supports that SWAP is not as sensitive as SAP for detecting glaucoma.
 228 They used a sub analysis of early glaucoma as defined by the CIRRUS OCT which had
 229 been modified to 'capture' early glaucoma at the expense of specificity. With this method
 230 they may however have included patients that otherwise would not have been considered
 231 with solely visual field assessment.

232

233 3.2 Frequency Doubling Technology (FDT)

234 The frequency doubling phenomenon was first described by Kelly over 40 years ago[17].
 235 When a low spatial frequency sinusoidal grating (<1 cycle/°) undergoes high temporal
 236 counter phase flickering at 15Hz or greater, gratings appear to double to twice their actual
 237 spatial frequency[47]. Essentially there is a rapid contrast reversal which light bars become
 238 dark and vice versa.

239 The frequency doubling phenomenon is thought to be mediated by a subset (five per cent) of
240 ganglion cells within the magnocellular pathway called M_y cells[18,48]. Similar to the blue-
241 yellow pathway cells the M_y cells have larger diameter axons making them more prone to
242 damage in early glaucoma[21,49]. In order for FDT to be effective the spatial frequency
243 should be between 0.1 and 4 c/deg⁻¹ (cycles per degree) and the temporal frequency greater
244 than 15Hz. Both are dependent upon retinal eccentricity in addition to a mean background
245 luminance of 50cd/m²[18,24]. This forms the rationale for the use of FDT to detect
246 glaucomatous field damage earlier than SAP.

247 **3.2.1 Test (Algorithm) choice**

248 FDT first came into use in 1997[50]. The first generation FDT manufactured by Welch Allyn
249 (Skaneateles Falls, New York, USA) used a 10° square stimuli, which was found to be
250 initially problematic as its large size prevented it from detecting small visual field
251 defects[24,51,52]. Second generation FDT was released in 2005 using a 5° square stimuli to
252 overcome this problem using the Humphrey Matrix visual field instrument[53,54]. The Matrix
253 test pattern was designed to be similar to the Humphrey Field analyser and Octopus
254 perimetry using a 0.43° round target on a 6° square matrix[50].

255 Screening programmes on the first generation FDT included the central 30 degrees of the
256 visual field. These algorithms used a modified binary search (MOBS) strategy. The algorithm
257 presents a grating at a level where 99% of normal subjects of an aged matched control
258 would see. If this is seen the zone is labelled normal, if this is not seen on a repeated
259 presentation then a grating at the 99.5% level is presented and increased until the stimulus
260 is seen[24,55]. The screening tests are performed in a supra-threshold pattern. Supra-
261 threshold is performed whereby the intensity of the stimulus shown is calculated to be above
262 the patient's threshold. Threshold is performed where the stimulus is decreased in intensity
263 using an adaptive staircase procedure until no response is given[56].

264 Subsequent test programmes have been developed to reduce the test time for FDT. They
265 include rapid efficient binary search (REBS) and zippy estimation of sequential testing
266 (ZEST)[55]. REBS is based on the MOBS strategy but requires two response reversals
267 whereas MOBS requires four[55]. ZEST uses a probability density function at each location
268 (the probability that each subject will have that threshold) with patient responses modifying
269 the probability density function until the standard deviation of the probability density function
270 becomes sufficiently narrowed[57]. The results of FDT tests have been compared to a
271 normative database of 700 eyes and can be age matched[58].

272 Isawe and colleagues [59] proposed that FDT could be an effective method of visual field
273 screening due to the short test time, its portability and relatively low-cost. Studies have
274 reported sensitivity for FDT ranging between 83% to 93% and specificities ranging between
275 55% to 100%[60-65]. FDT also appears to have lower test-retest variability and less of a
276 learning effect which makes it a promising emerging psychophysical test[66].

277 **3.2.2 Abnormality Criteria**

278 FDT is similar to SWAP in that definitive criterion for what is defined as normal and abnormal
279 has not been uniformly decided upon. As Matrix FDT was released in 2005 there remains a
280 lack of large population longitudinal studies to assess what criteria would be most
281 discriminatory for a glaucoma diagnosis. Different criteria have been suggested although the
282 view for abnormal criteria appears to be reaching a more uniform decision compared with
283 SWAP.

284 Fogagnolo *et al.* [67] propose that the presence of at least one point at the $P < 5\%$ level on
285 the pattern deviation plot (PDP) on the N-30 or C-20 screening programme is the most
286 suitable criteria for detecting glaucoma. Six different classifications of a defect were used
287 and analysed by receiver operator characteristic curves (ROC). A ROC curve plots true-
288 positive rate against the false positive rate[68]. The area under a ROC curve of 1 gives
289 100% sensitivity and specificity whereas a ROC of 0.5 would indicate no diagnostic
290 value[47]. The more stringent of the criteria did not significantly have a higher sensitivity or
291 specificity for detecting glaucoma which explains the author's choice of defect criteria in
292 order to capture most glaucomatous loss. Patients included in the study had POAG to
293 enable the authors to identify the most sensitive and specific criteria for diagnosing
294 glaucoma. Definitions for glaucoma defects on SAP were in accordance with the guidelines
295 recommended by Hodapp-Parish-Anderson[70] which are also currently used by the
296 National Collaborating Centre for Acute Care [36] in the United Kingdom. The results for
297 sensitivity and specificity for visual field loss was comparable to those of others [63, 71-73]
298 and particularly in moderate and advanced glaucoma cases. Notably the authors found that
299 the screening programmes C-20 and N-30 showed a lower sensitivity for detecting nasal
300 step defects; one of the most common glaucomatous defects[70].

301 Brusini *et al.* [74] suggest PSD $< 5\%$ and/or at least two areas on the PDP $P < 5\%$ should be
302 used as the cut off criteria for the N-30 programme using the first generation FDT. Their
303 results with these diagnostic criteria were similar to those previously reported by Weinreb,
304 Medeiros & Sample [75] for the same programme.

305 A small cross sectional comparative study by Hong *et al.* [76] also suggest using more than
306 five points in the PDP at the $P < 5\%$ level to discriminate between glaucomatous and non-
307 glaucomatous fields. This classification is more stringent than those proposed by Fogagnolo
308 *et al.* and Brusini *et al.* [67,74]. Hong and associates allowed for the influence of cataract on
309 visual field testing [77] which had not been accounted for in previous studies. All subjects
310 included in the study had manifest POAG detectable on SAP which were termed as early
311 defects i.e. MD not worse than -6dB. Both the normal and POAG group had a mean age of
312 under 40 which is significant as it is more likely that older individuals than in this age group
313 would be routinely screened for glaucoma[78]. ROC curves were used to analyse the criteria
314 proposed by the authors (MD $P < 1\%$ and PSD $P < 5\%$) and appropriate statistical testing was
315 used. There was however a significant difference in the depth of defect between the control
316 group and the study group suggesting the criteria may be useful but only in the age range of
317 the population studied. Further work is required using these criteria for predicting visual field
318 loss in at risk groups and for the learning effect to be taken account for when considering a
319 cut-off point.

320 Choi, Lee & Park [66] examined the use of the Humphrey Matrix perimeter for the detection
321 of pre-perimetric glaucoma and to define a clinically useful cut-off point. A strength of the
322 study is that the learning effect was allowed for both SAP and FDT by giving each patient
323 two practice attempts. Their initial ophthalmic investigation also included all gold standard
324 tests as defined by the National Collaborating Centre for Acute Care[36]. ROC curves were
325 used to determine which parameter (MD or PSD) provided the best discriminating power.
326 PSD was found to be the best discriminator which is in agreement with Hong *et al.*[76].

327 Abnormality criteria are essential for defining a glaucomatous visual field when screening. As
328 is the current situation with SWAP, definitive criteria have not been agreed upon. However
329 evidence currently published does not show as much variation as what 'abnormal' should be
330 defined as on FDT when compared to defining SWAP abnormality criteria. There is a need
331 for more longitudinal studies taking into account for the variances that occur in the screening
332 population, the age of patients performing the test and where the criteria produce repeatable

defects. A summary of the studies attempting to define abnormality criteria is shown in Table 2 for direct comparison.

Table 2. Summary of studies attempting to define abnormality criteria for FDT.

Study	First Generation or Matrix FDT	Sample Size	Control Group Used	Suggested Abnormality Criteria	Follow up Period
Fogagnolo <i>et al.</i> 2005 [67]	First generation	40 eyes	40 eyes	At least one point at P<5% on the PDP	Not reported
Brusini <i>et al.</i> 2006 [55]	First generation	258 eyes	60 eyes	PSD <5% and/or at least two areas on PDP at P<5%	Not reported
Hong <i>et al.</i> 2007 [76]	Matrix	36 eyes	24 eyes	More than 5 points on PDP at P<5%	Not reported
Choi, Lee & Park 2009 [66]	Matrix	99 eyes	122 eyes	PSD of greater than -3.14dB	Not reported

3.2.3 FDT and SAP

Few studies exist that longitudinally compare FDT with SAP in respect to whether a subject who presents with a defect on FDT would proceed to develop a defect on SAP. Many of the early studies looking at agreement between FDT and SAP were conducted with subjects who already had detectable manifest glaucoma[79,80].

A small prospective study by Quaranta *et al.* [81] examined the concordance of first generation FDT with SAP in 25 manifest glaucoma patients and 25 ocular hypertensives using MD plots; a measure of overall sensitivity loss. Although the study indicated a significant correlation between MD in the glaucoma and ocular hypertensive group, they also compare PSD but with no results presented other than 'it was significant between groups'. There was no classification given as to what defines a visual field as glaucomatous or not which makes it difficult to draw conclusions from. No follow up was performed in this study to ascertain whether the defects persisted on repeated testing or whether the subjects showing FDT defects in the ocular hypertensive group went on to produce defects on SAP.

In a larger study by Racette *et al.* [82] on 80 eyes, they found that first generation FDT was better able to detect early glaucomatous damage than SAP using ROC analysis. Mean deviation for SAP and PSD <5% for first generation FDT were found to be the best indicators of early glaucomatous damage. However, there are issues with their definition of their normal pressure. Routinely a pressure under 21mmHg is considered normal yet a cut-off upper pressure of 23mmHg was used. The study has an advantage over the smaller study by Quaranta and colleagues as they provide parameters to classify glaucomatous loss and check for persistence of defects. Furthermore, they acknowledge the limitations of their study and for longitudinal change, further studies are required.

Medeiros and associates[83] reported that first generation FDT defects were predictive of future SAP defects in a longitudinal observational study over 17 months. The subjects were

362 retrospectively taken from a larger study (Diagnostic Innovations in Glaucoma Study) but
363 were not taken at random from the study group: the purpose being to include only subjects
364 at risk of developing POAG and not from secondary causes e.g. pigment dispersion
365 syndrome. This potentially introduces selection bias. It is interesting to note that the age
366 range of the sample taken is not given yet the authors found a statistically significant
367 difference between the age of subjects who converted and those who did not. The lack of
368 age range renders it difficult to consider the results for the population at risk. However, gold
369 standard tests were used to exclude manifest glaucoma as per National Collaborating
370 Centre for Acute Care guidelines [36] and allowances were made for learning effect[84].
371 More importantly the fields were repeated at follow up to determine if the defects persisted.
372 To reduce the influence of intra test variability and for a defect to be confirmed on SAP the
373 field was repeated three times. A normal database was used from a previous study
374 conducted by the authors in normal individuals and found 94% specificity upon using their
375 definition of an abnormal FDT (two points on MD $P < 5\%$ level or a PSD of $P < 0.05\%$).
376 Fourteen out of the 105 eyes studied progressed to repeatable defects on both SAP and
377 FDT with the locations of the defects correlating. The results of this study show promise in
378 terms of a possible prediction of the development of SAP defects by location of repeatable
379 defects on FDT.

380 Spry, Hussin & Sparrow[80] compared the use of matrix FDT 24-2 threshold strategy with
381 the 24-2 SITA-Fast programme available on the HVF. The study was larger than that of
382 Quaranta *et al.* [81] and all patients went through gold standard assessment for detection of
383 glaucoma (SAP, gonioscopy, tonometry and optic nerve head examination)[36]. A strength
384 of the study was the classification of subjects into subgroups based on clinical examination
385 separating out the different types of glaucoma and suspects. In contrast to the Quaranta
386 study[81] the mean age of the study group was more representative of the patients
387 undergoing glaucoma testing. Upon comparison of MD and PSD moderate agreement was
388 found between the two techniques by means of a ROC analysis. The criteria used to define
389 a glaucomatous field were liberal and based upon clinical decision in order for it to be
390 applied to the clinical environment and the authors acknowledge that this may have led to
391 the high sensitivity found. Spry and associates[80] suggest that for the purposes of
392 glaucoma screening sensitivity should be compromised in order to optimise the specificity
393 and positive predictive value of FDT. In order to confirm the results further follow up is
394 required to consider whether individuals who are screened with matrix FDT with the 24-2 test
395 pattern do develop defects that are synonymous with SAP.

396 **3.3 FDT and SWAP**

397 Both SWAP and FDT have been recognised as potential methods for the detection of early
398 glaucoma. Studies have looked at the comparability of FDT with SWAP with respect to
399 sensitivity and specificity and concordance with each other[27,46,85-89].

400 Landers and associates[85] reported that FDT and SWAP are comparable in terms of
401 sensitivity, specificity and concordance. Spry *et al.* [80] examined the diagnostic capability of
402 both SWAP and FDT. They reported that FDT had a lower test-retest variability (39% SWAP
403 compared to 34% FDT) but both methods had similar abilities in detecting early glaucoma.
404 One issue with the comparison is that FDT was not performed using the Welch Allyn nor
405 matrix FDT perimeter but on a 'custom device'. Thus it is difficult to compare their results
406 with other studies using standard rather than customised assessments. Specifically, the 24-2
407 test pattern used for their FDT was a 4° diameter square which is not used in either the
408 Welch Allyn or matrix perimeter[50,51]. Gold standard tests were used however to classify
409 glaucoma and pattern deviation was used to classify defects rather than total deviation; the
410 latter providing a generalised impression of field loss. The use of PD or PSD is also
411 supported by Leeprechanon *et al.* [27] who found that, for matrix FDT, this provided the best

412 sensitivity and specificity. As for SWAP there is not a definitive definition of 'abnormal' as
413 previously discussed.

414 A prospective study by Horn *et al.* [87] attempted to overcome the limitations of previous
415 studies in order to determine whether SWAP and first generation FDT are able to detect pre
416 perimetric glaucoma, with interesting results. A double-bagging technique was used in the
417 study. The previous studies by Landers *et al.*, Soliman *et al.* and Spry *et al.* [47,80,85] relied
418 upon making a clinical judgement regarding the outcome of the visual field testing. By using
419 the double bagging technique this standardises the outcome for all participants with all fields
420 being treated in the same way. Horn *et al.* [87] recognised that the numbers assessed in
421 their study might not be sufficient to produce the most accurate, reliable or efficient algorithm
422 and therefore requires a larger study. The method itself may facilitate future study and allow
423 this area of research to finally move forward.

424 Matrix FDT was compared with SWAP in a prospective case-control study by Leeprechanon
425 *et al.* [7]. The results showed a significant correlation between FDT and SWAP using MD and
426 PSD with FDT showing a higher sensitivity of detecting glaucoma (72% versus 54%). The
427 sample size was small, however the 24-2 test pattern used for both FDT and SWAP allowed
428 for a more direct comparison of results. A strength of the study was that concordance of the
429 location of the defect was investigated with a 72% agreement reported. When considering
430 the indices PSD and PD at the P<5% level they were significantly higher in the early
431 glaucoma group versus the normal group on FDT but not on SWAP suggesting that FDT
432 may be better at filtering out the generalised noise which is known to occur in SWAP.

433 More recently Liu *et al.* [46] found matrix FDT to be more sensitive than SWAP in detecting
434 glaucoma at comparable levels of specificity. The criteria used for defining an abnormal
435 visual field for FDT and SWAP was the same as that for SAP for which there is contention as
436 to whether SAP criteria can be used for other visual field assessment methods[26,66].
437 Furthermore, the confidence intervals overlapped for matrix FDT and SWAP results which
438 may indicate that there is little difference in the diagnostic abilities of SWAP and matrix FDT.
439 A subgroup analysis was performed with patients with 'early glaucoma' but no definition of
440 early glaucoma was provided. The results reported by Liu *et al.* [46] were in agreement with
441 those of Leeprechanon *et al.* [27] in their larger sample size.

442

443

444 **4. CONCLUSION**

445

446 With an aging population and the rise in the prevalence of glaucoma worldwide there is a
447 clear need for rapid diagnosis to commence treatment early to preserve both vision and
448 visual field. The need for rapid diagnosis however does need to be considered from an
449 economic perspective i.e. is the time and money spent on diagnosing glaucoma earlier
450 clinically useful providing the best cost: benefit ratio.

451

452 There is evidence available to show that SWAP, first generation and matrix FDT have
453 potential as psychophysical tests for earlier glaucoma detection. SWAP has been
454 investigated at a greater length than the more recently emerging FDT methods. Both SWAP
455 and FDT lack defined abnormality criteria like those that exist for SAP. Until this is
456 established it is difficult to determine whether or not the tests have a role in either glaucoma
457 screening in the community or at the first visit to the hospital eye service. SWAP has the
458 issue of a large inter and intra subject variability requiring up to five attempts before the
459 patient becomes sufficiently reliable. This has time and economic implications which need to
460 be considered. FDT shows less variability with more repeatable results and lesser learning

effect. The testing time is also short with FDT which again may make it a more favourable test than SWAP.

SWAP and FDT on direct comparison have been found to have similar sensitivity and specificity in predicting glaucomatous visual field loss and show moderate agreement with SAP for detecting field loss. Few studies however consider whether the defects correlate between tests and, in SWAP and FDT, whether the defects develop in the same location as that in SAP. This is a question requiring further research given that SWAP (which uses blue stimuli to isolate the S cones and K pathway) may be more relevant to central perimetry within 10 degrees of fixation whereas FDT (which uses fast reversal, large contrast stimuli to isolate the M pathway) may be more relevant to perimetry peripheral to the central 10 degrees. There is a lack of longitudinal studies addressing persistence of defects and anatomical correlation of defects to be able to definitively ascertain the clinical application of both FDT and SWAP. Further research is thus recommended to answer these outstanding questions.

To conclude both SWAP and FDT could potentially be used as methods for earlier glaucoma detection but require well-defined, consistent abnormality criteria within specified testing algorithms. Currently, standard automated perimetry remains the preferred choice for clinical assessment until such time that evidence shows SWAP and/or FDT techniques to be superior in respect to accuracy and reliability in the detection of early visual field loss in glaucoma.

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491 **COMPETING INTERESTS**

492

493 The authors have declared that no competing interests exist.

494

495 **AUTHORS' CONTRIBUTIONS**

496

497 Author JMB designed the study, performed the review and wrote the drafts of the
498 manuscript. Author FR provided oversight for the review and contributed to the drafts of the
499 manuscript.

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502 **CONSENT (WHERE EVER APPLICABLE)**

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504 Not applicable.

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507 **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**

508

509 Not applicable.

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