Iowa Institute in Biostatistics 2010
Department of Biostatistics
University of Iowa

Study of Glaucoma Change Probability for Open-angle Glaucoma

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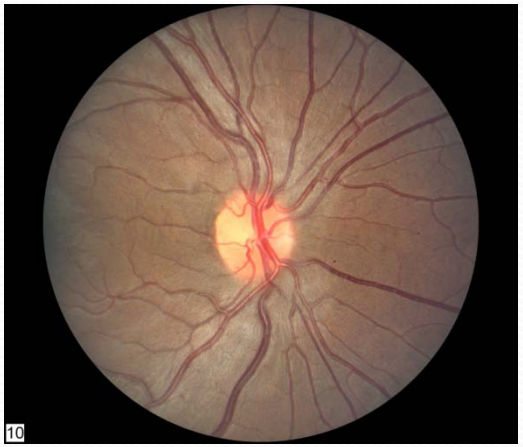
Outline

- Background and Significance
- Objectives
- Methodology
- Results and Discussion
- Conclusion
- Future work
- Acknowledgements

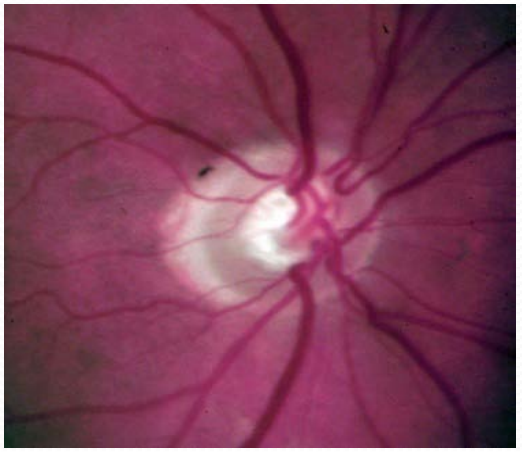
Background and Significance

What is Glaucoma?

- Glaucoma is a sight-threatening disorder marked by an increase in intraocular pressure (IOP) that is too high for the optic nerve to tolerate.



- It is the most common optic nerve disorder, affecting 1-2% of the US population and one of the leading causes of blindness.[1,2]



- There are two types of glaucoma: open angle and closed angle.

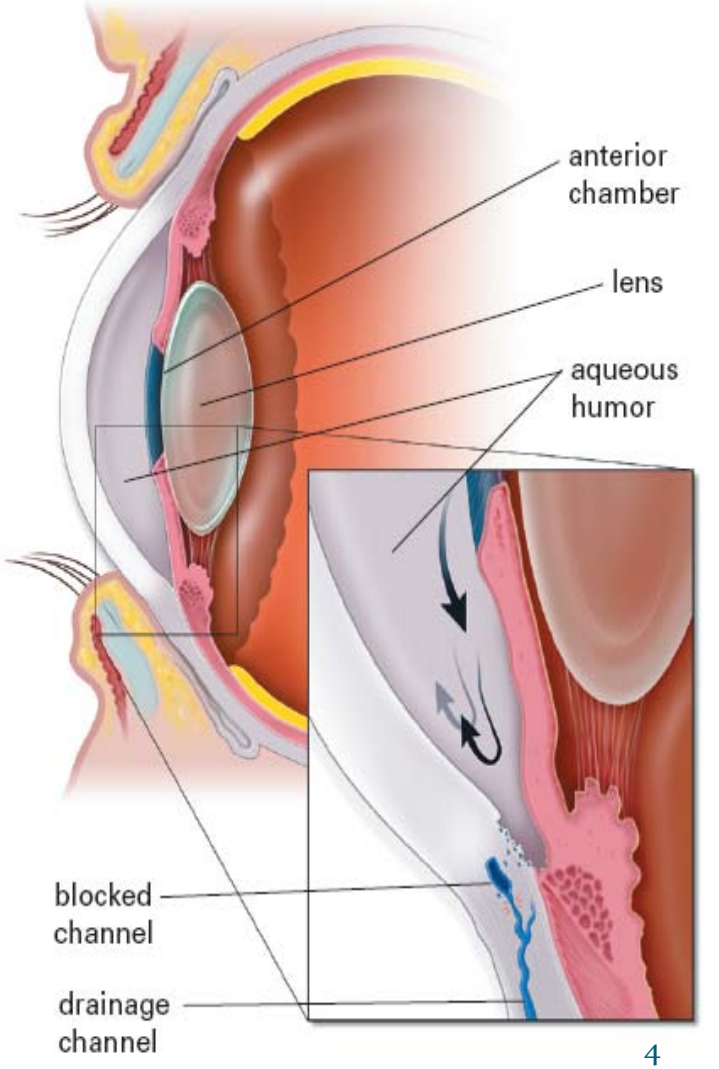
- The number of persons estimated to be blind as a result of primary glaucoma is 4.5 million, accounting for slightly more than twelve percent of all global blindness[3].

Background and Significance

What is Glaucoma?(Cont'd)

- Open angle glaucoma
  - Excessive buildup of aqueous humor, increasing IOP.
  - When IOP remains elevated or continues to rise, fibers in the optic nerve are compressed and destroyed, leading to a gradual loss of vision over a period of years

- Closed angle glaucoma
  - Is relatively uncommon.
  - Primarily characterized by rapid and extreme elevations of IOP, often causing acute symptoms such as severe eye pain and rapid blurring of vision[1].



Perimetry Test (Quantification of VF)

Perimetry Test (Quantification of VF)

Analogy

Single Field Analysis | PRE-LAUNCH EVALUATION SOFTWARE. | Eye: Right

Name: Z CARDONA, GLORIELL | DOB: 09-13-1987

ID:

Central 24-2 Threshold Test

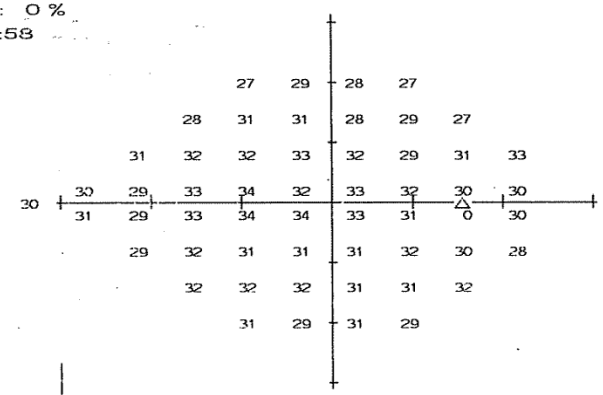
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/10
False POS Errors: 0 %
False NEG Errors: 0 %
Test Duration: 02:58

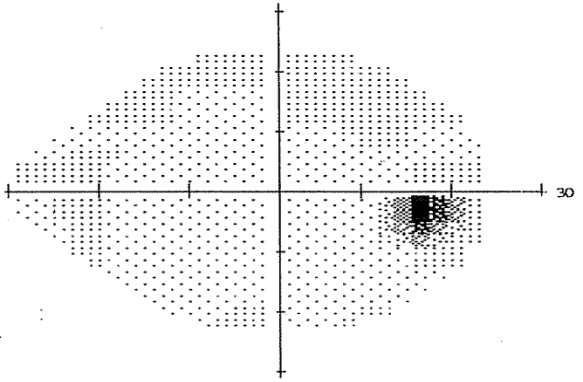
Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Fast

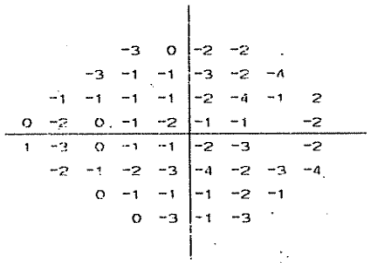
Pupil Diameter: 7.5 mm
Visual Acuity:
RX: DS DC X

Date: 07-20-2010
Time: 9:23 AM
Age: 22

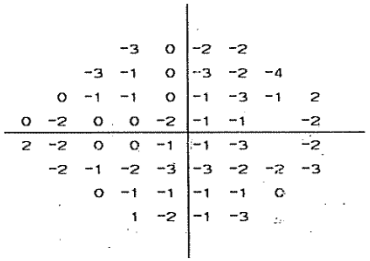
Fovea: 34 dB ::







Total Deviation

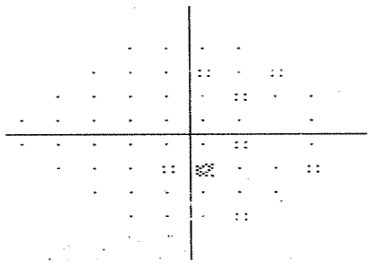


Pattern Deviation

GHT
Within normal limits

VFI 100%

MD -1.55 dB P < 10%
PSD 1.21 dB



:: < 5%
< 2%
< 1%
< 0.5%

Visual Field Laboratory
University of Iowa
College of Medicine
Iowa City, IA
(319) 356-1611

HFA II 750-10127-4.2/4.2

Single Field Analysis | PRE-LAUNCH EVALUATION SOFTWARE. | Eye: Right

Name: Z RIBERA, VANESSA
ID:
DOB: 10-19-1990

Central 24-2 Threshold Test

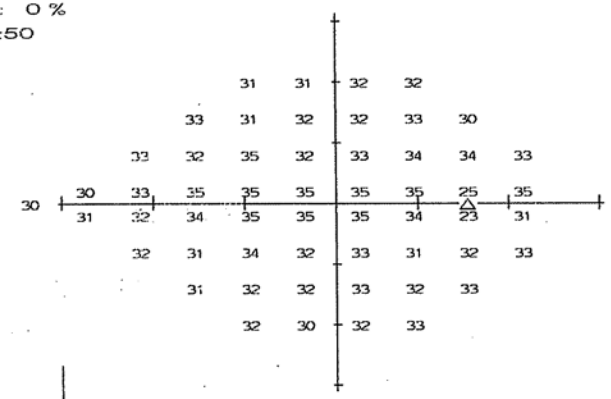
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/12
False POS Errors: 0 %
False NEG Errors: 0 %
Test Duration: 02:50

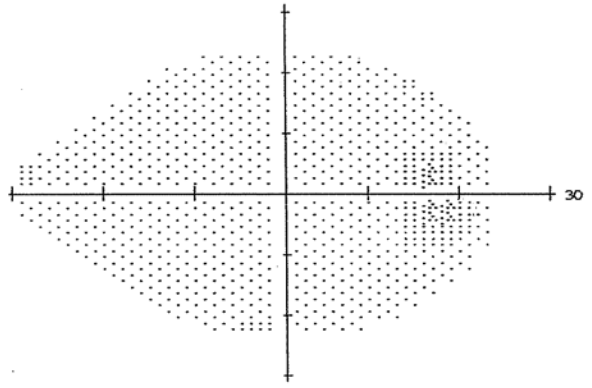
Fovea: 39 dB

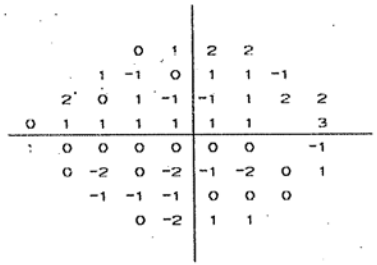
Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Fast

Pupil Diameter: 6.6 mm
Visual Acuity:
RX: DS DC X

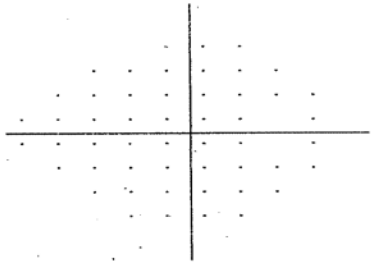
Date: 07-20-2010
Time: 9:42 AM
Age: 19

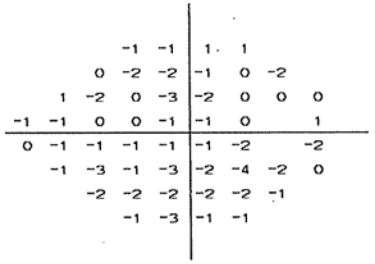




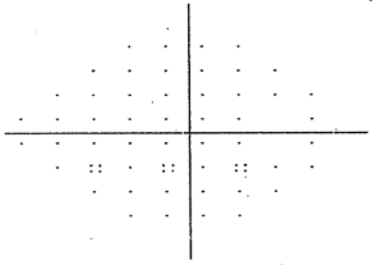


Total Deviation





Pattern Deviation



:: < 5%
▒ < 2%
▓ < 1%
■ < 0.5%

GHT
Within normal limits

VFI 100%

MD +0.16 dB
PSD 1.13 dB

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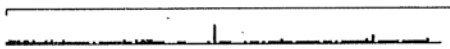


HFA II 750-10127-4.2/4.2

Background and Significance

Methods for detecting change/disease progression at a visual field location

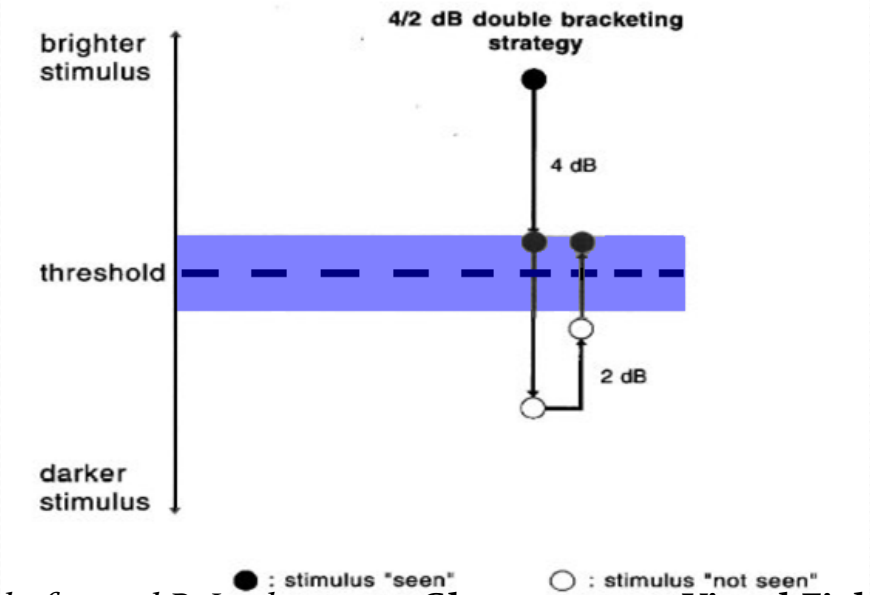
- Point wise regression on the 52 locations over time to identify decrease in regression slope

- Glaucoma Change Probability (GCP)
  - Examines the difference in threshold deviation at individual locations between a given field and baseline test results
  - The baseline test result is obtained through a test retest mechanism
    - 32 patients were tested once every week for 5 weeks
      - Repeated testing of both normal and patients with varying degrees of visual loss.
      - Construction of confidence limits for retest variability.

Methods for detecting light sensitivity threshold

Staircase procedure

- Begins from high intensity stimulus and it is reduced until the observer makes a mistake in which case the procedure is reversed and then increased until observer responds correctly.



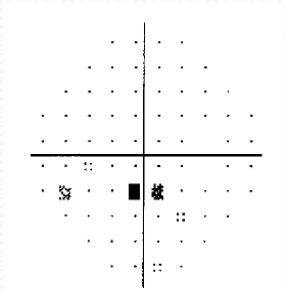
Perimetry Test (Quantification of VF)

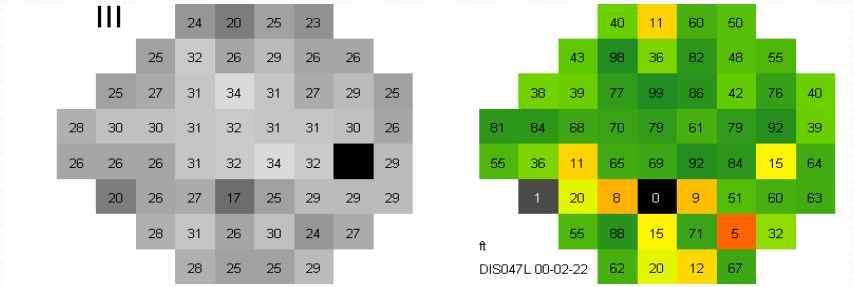
M. Schaumberger, B. Schafer, and B. Lachenmayr. **Glaucomatous Visual Fields** FASTPAC Versus Full Threshold Strategy of the Humphrey Field Analyzer. Investigative Ophthalmology & Visual Science, 1995, Vol. 36, No.7

Analogy

This is similar to two other optimization methods:

- Escalation/ De-escalation in Clinical Trials to reach MTD
- Stochastic Approximation in Statistics

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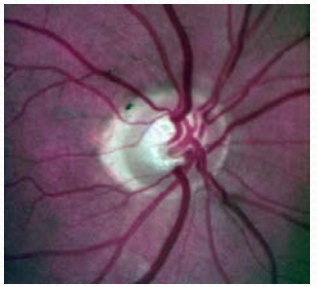

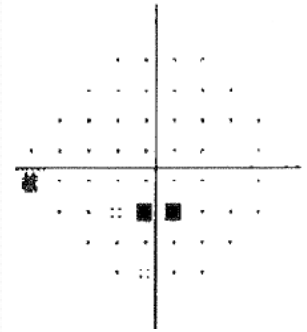

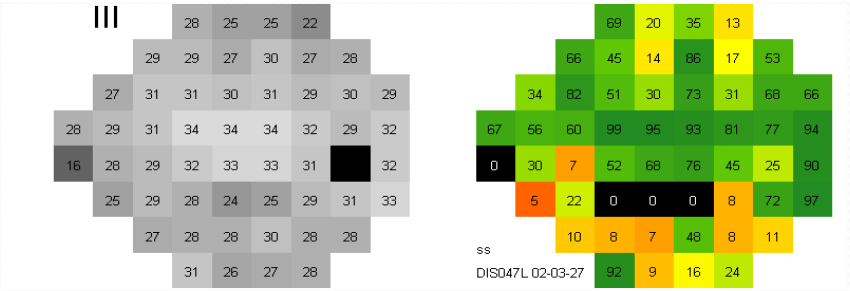
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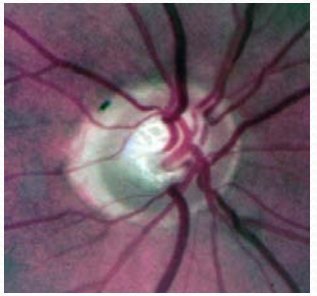

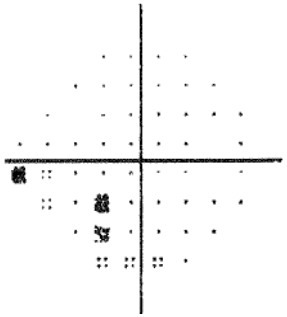

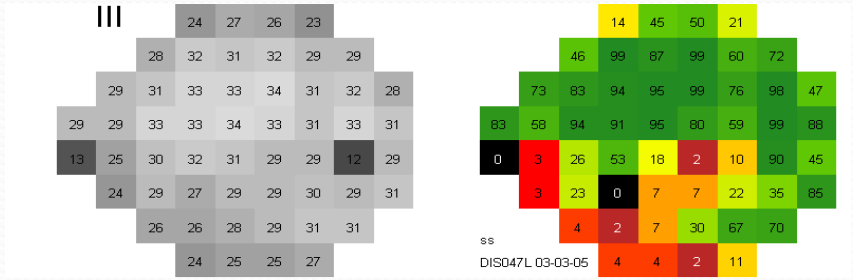
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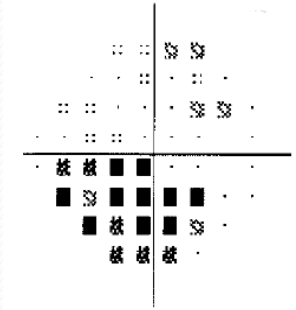


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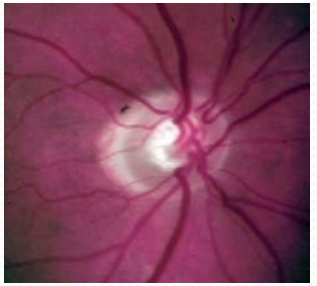
DIS047L 06-10-12



Objectives

- To program and compare the performance of three variants of GCP on longitudinal clinical data gathered at the University of Iowa department of neurology.
  - 120 glaucoma subjects and 60 normal subjects
- Each of these variants is characterized by the following:
  - Threshold crossing from a test-retest baseline data gathering (probabilistic)
  - Confirmation of threshold crossing on overlapping (not necessarily spatially contiguous) visual fields in time (clinician input)
  - Number of locations affected in a visual field (clinician input).

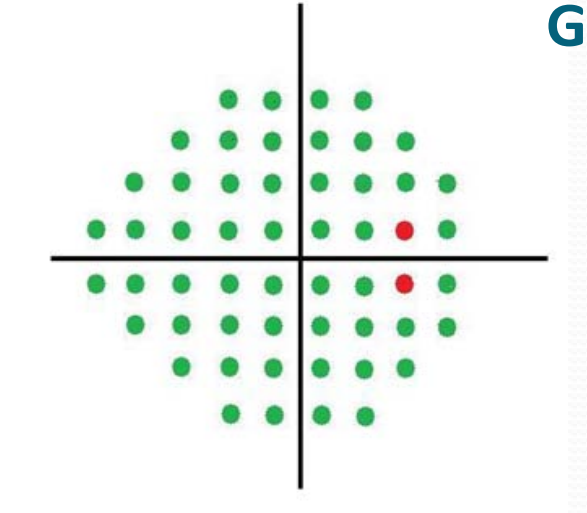
Methodology

GCP Methods Considered

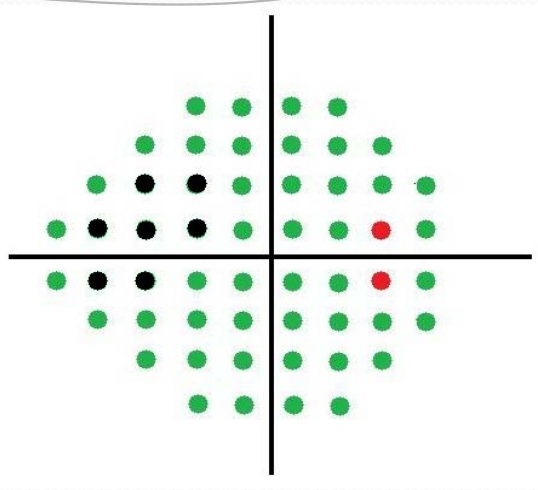
Criteria for progression / change assessment

- GCP(2x4): 4 or more locations fall below a threshold and are confirmed at the next two tests
- GCP(8,2x4): 8 or more locations fall below a threshold and are confirmed at one of two tests
- GCP(3x4): 4 or more locations fall below a threshold and are confirmed at the next three tests

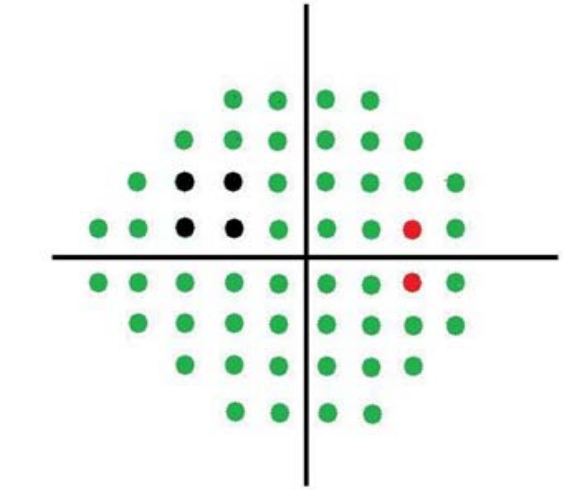
GCP(2x4)



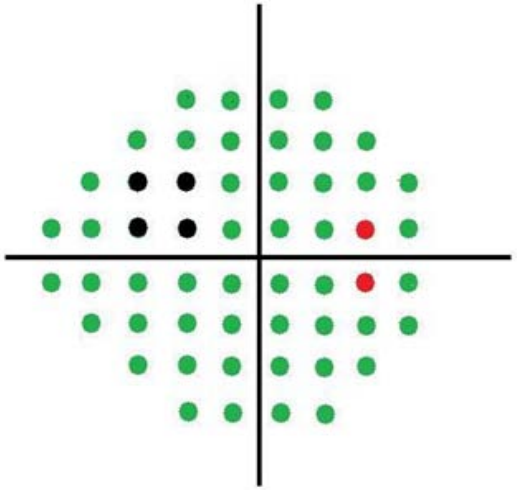
Normal Eye



Test #1

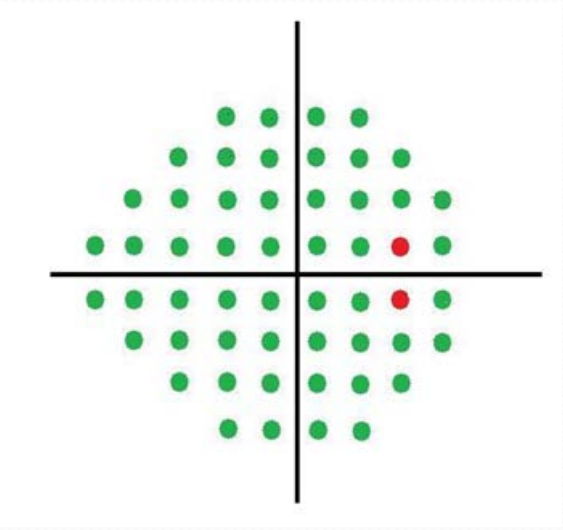


Test #2

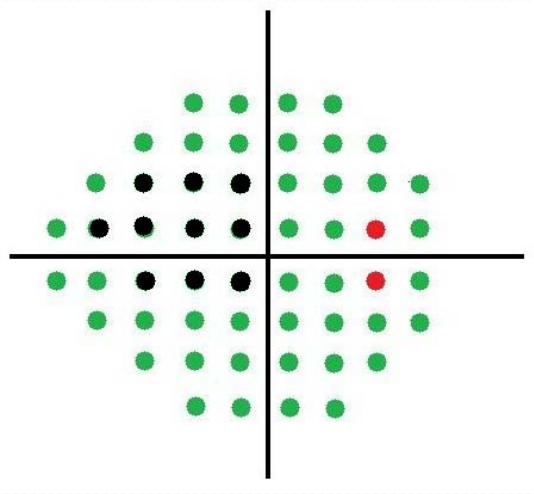


Test #3

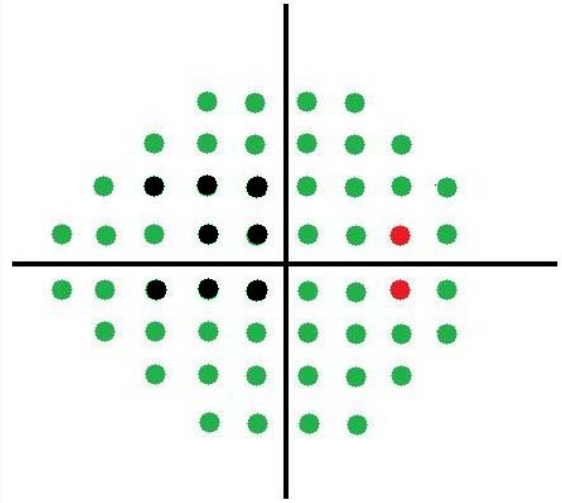
GCP(8,2x4)



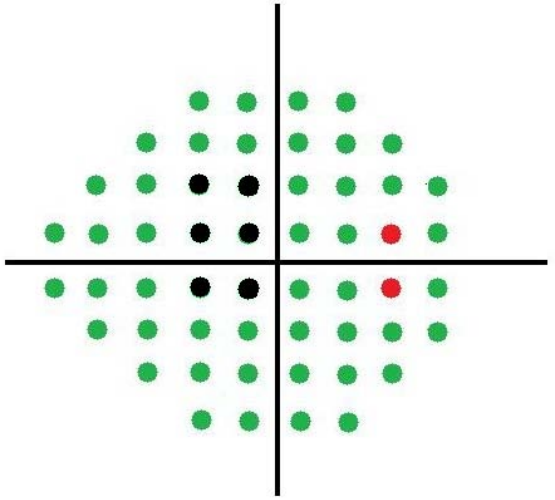
Normal Eye



Test #1

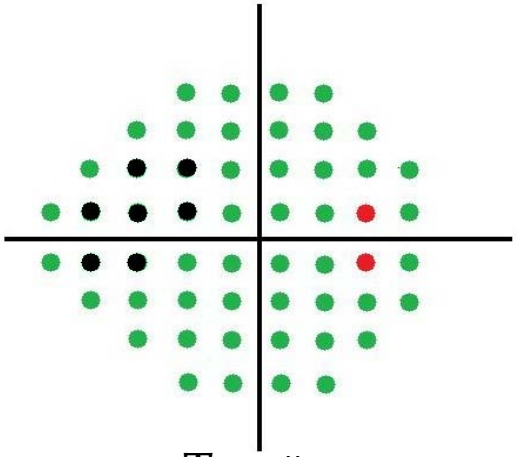


Test #2

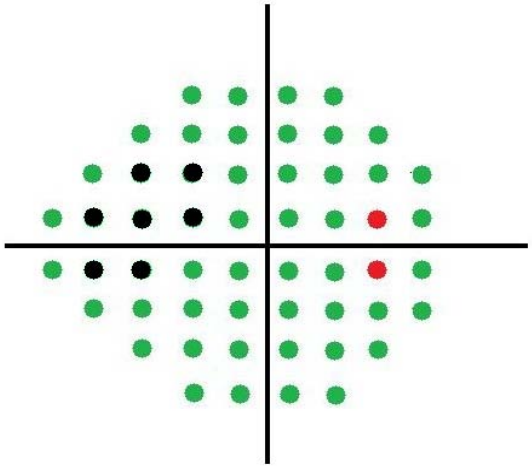


Test #3

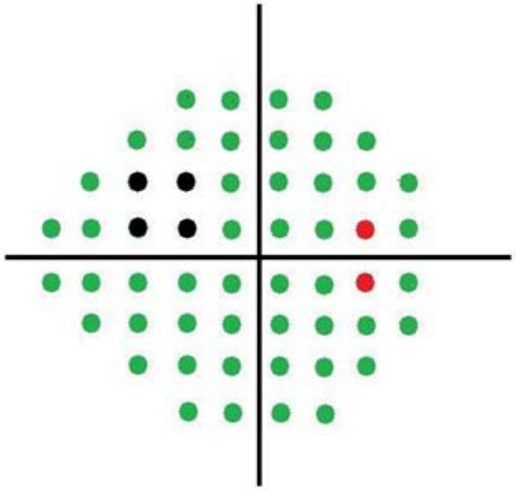
GCP(3x4)



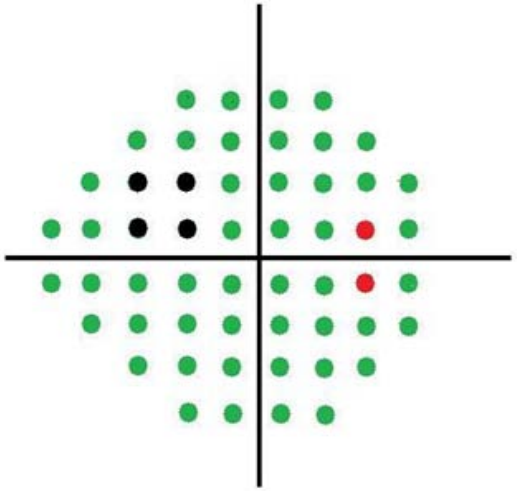
Test #1



Test #2



Test #3



Test #4

Methodology

Basis for comparing GCPs and ROC

- Since the data is highly variable, it is necessary to determine which GCP method has the highest sensitivity and specificity.
- A receiver operating characteristic (ROC) curve illustrates the relationship between sensitivity and specificity.

Methodology

Datasets

- 120 subjects with glaucoma (4 year period, every 6 months)
- 60 subjects with no disease (control)
- 32 test-retest subjects for constructing the threshold confidence interval
- 3 functions were written for obtaining the sensitivity and specificity of each GCP method and comparing their efficiency.

Methodology: **R Code**

```
# Create function with patient number and population to get any patient's data
GCP <- function(i, population, q_trt){
  M <- subset(population,PNUM==i)
  NewM=M[,-1]
  avg_population<-colMeans(NewM[1:2,])
  population_avg <- rbind(avg_population, NewM[3:10,])
  result <- (population_avg < q_trt)
  N <- t(result[,-c(26,35)])
  prog.2by4 <- 0
  prog.3by4 <- 0
  prog.8_2by4 <- 0
  for(i in 1:7) {
     P <- data.frame(unname(N[, i:(i + 2)]))
      v <- rowSums(subset(P, X1 == 1))
      if(length(v[v>=2]) >= 4) { prog.2by4 <-1 }
      if(length(v[v==3]) >= 4) { prog.3by4 <-1 }
      if(sum(colSums(P, na.rm = TRUE), na.rm = TRUE)>=8 & length(v[v>=2]) >= 4) { prog.8_2by4 <-1 }
    }
   return(c(prog.2by4, prog.3by4, prog.8_2by4))
}
```

R Code (Cont.)

```
# Create a function to calculate the specificity and the sensitivity

DT<-function(quant) {
  q_trt=matrix(quantile(c(as.matrix(test_retest)),quant),9,54)
  R_glaucoma<-matrix(NA,120,3)
  for (i in 1:120) {R_glaucoma[i,]<-GCP(i+3000,glaucoma,q_trt)}
  R_normal<-matrix(NA,60,3)
  for (i in 1:60) {R_normal[i,]<-GCP(i+3000,normal,q_trt)}
     sens.2x4<-sum(R_glaucoma[,1])/120
     spec.2x4<-1-sum(R_normal[,1])/60
     sens.3x4<-sum(R_glaucoma[,2])/120
     spec.3x4<-1-sum(R_normal[,2])/60
     sens.8_2x4<-sum(R_glaucoma[,3])/120
     spec.8_2x4<-1-sum(R_normal[,3])/60
  return(c(sens.2x4, spec.2x4, sens.3x4, spec.3x4,sens.8_2x4, spec.8_2x4 ))
}
```

R Code (Cont.)

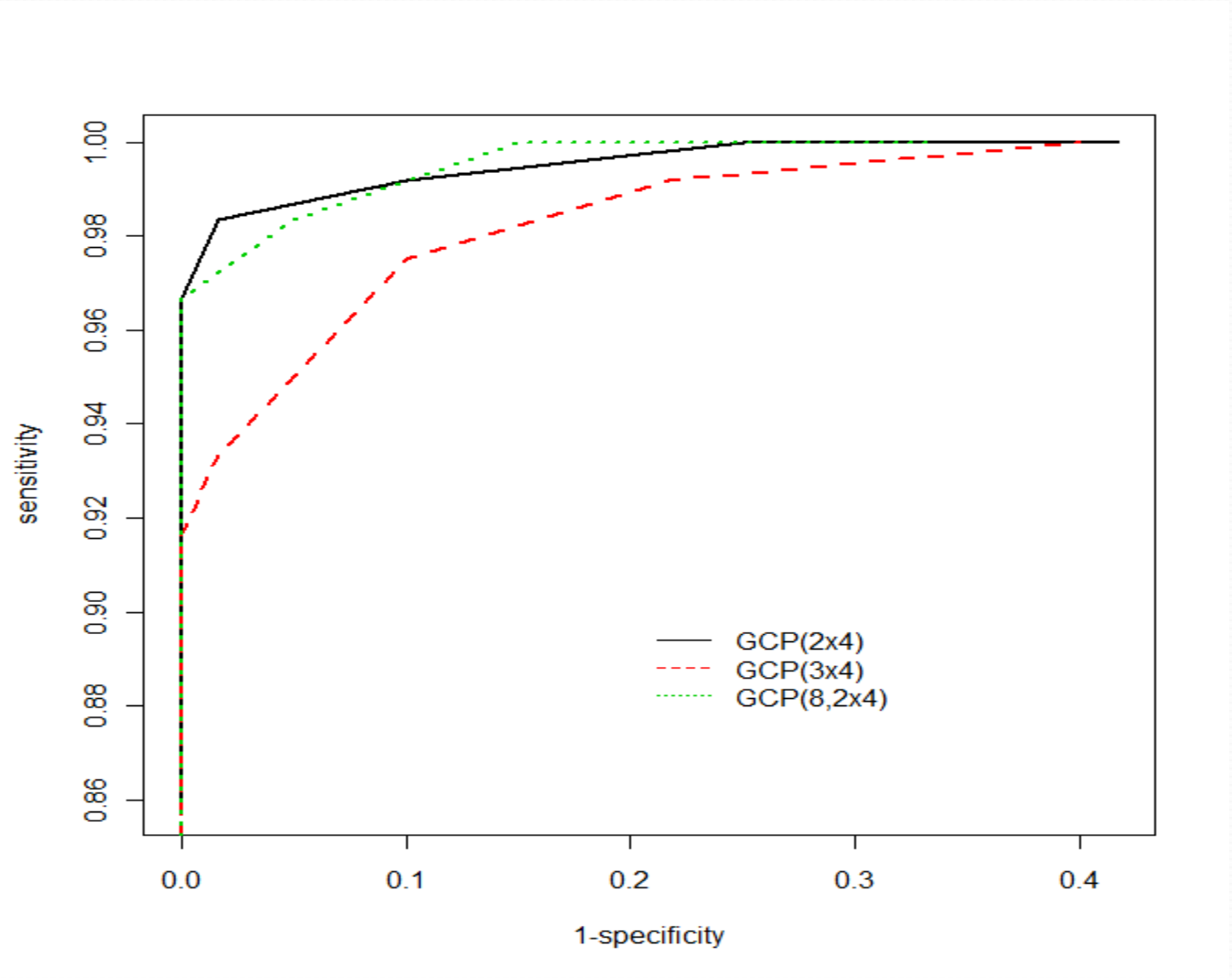
```
# Compute sensitivity and 1- specificity for each method over the percentile range of .70 and .90

v <- seq(0.70, 0.90, 0.01)
GV <- matrix(NA, length(v), 6)
for(i in 1:length(v)) {
  GV[i, ] <- DT(v[i])
}
VG <- data.frame(cbind(v, GV))
colnames(VG) <- c("quant", "sens.2x4", "spec.2x4", "sens.3x4", "spec.3x4", "sens.8_2x4", "spec.8_2x4")

plot(1-GV[,2],GV[,1], main="",xlab="1-specificity",ylab= "sensitivity" , col=1,lty=1,type="l", lwd=2)
lines(1-GV[,4],GV[,3], col=2,lty=2,type="l", lwd=2)
lines(1-GV[,6],GV[,5], col=3,lty=3,type="l", lwd=2)
legend(0.2, 0.9, bty = "n", lty = 1:3, col = 1:3, c( "GCP(2x4)" , "GCP(3x4)", "GCP(8,2x4)"))

# Create a function to compute the area under the ROC curve
A <- function(dat)   {
dat <-rbind(c(0,1),dat,c(1,0))
colnames(dat) <- c("sensitivity", "specificity")
return(aucRoc(dat))
 }
  A(GV[,1:2])
  A(GV[,3:4])
  A(GV[,5:6])
```

Results


sensitivity
1.00
0.98
0.96
0.94
0.92
0.90
0.88
0.86
0.0
0.1
0.2
0.3
0.4
1-specificity
GCP(2x4)
GCP(3x4)
GCP(8,2x4)

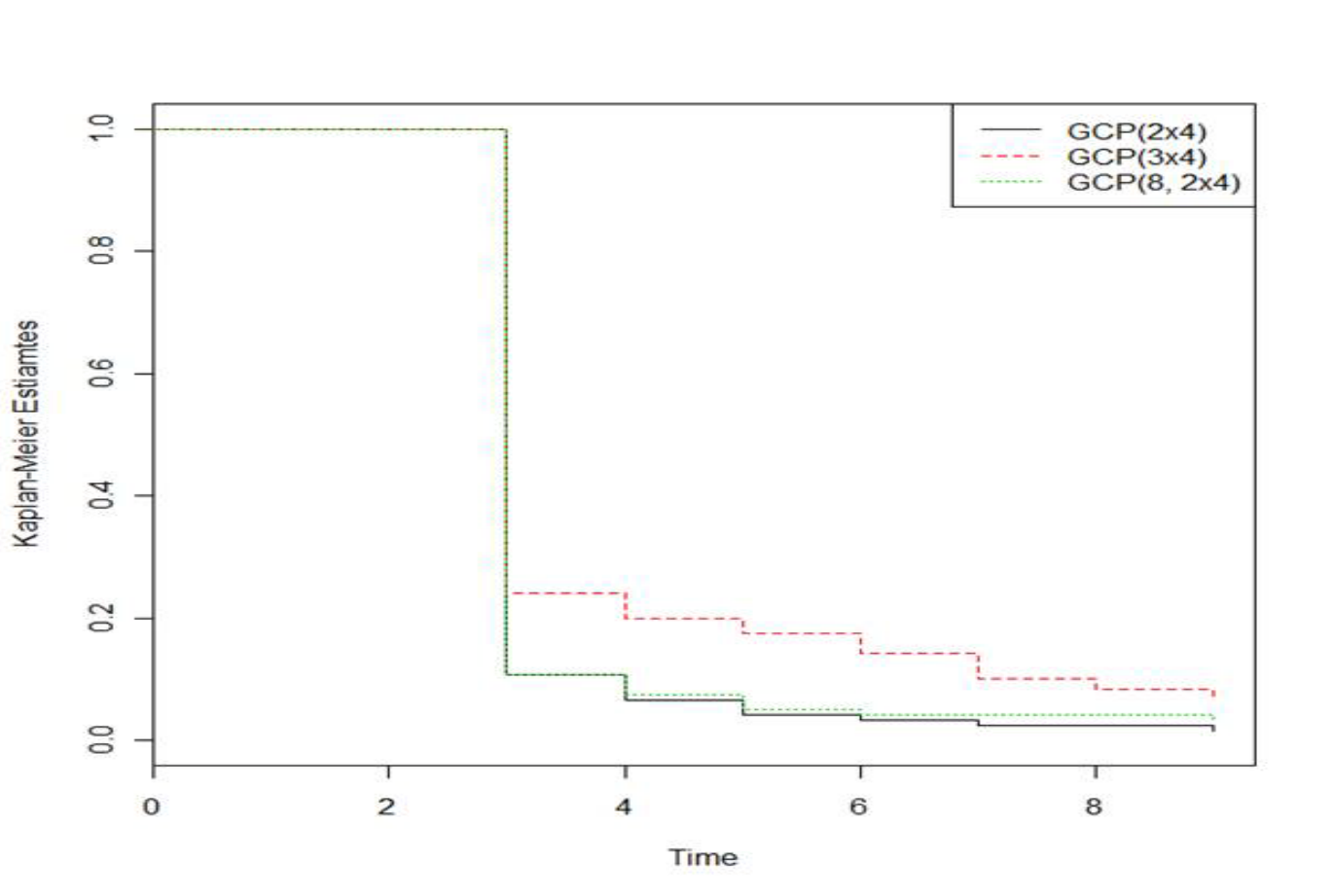
Results and Discussion

- According to the ROC curves, GCP(2x4) and GCP(8,2x4) show the highest sensitivity and specificity.
- Data analysis suggests that optimal lower bound is between .82 and .85

Which one detects change first?

- We examine all three methods in a Kaplan-Meier (KM) analysis
- We record the time each method signals a change
- Event is change/progression
- Subjects are censored if they don't show change by the end of study (9^{th} time point)
- The stratified KM plots provide a pictorial representation

Which one detects change first?



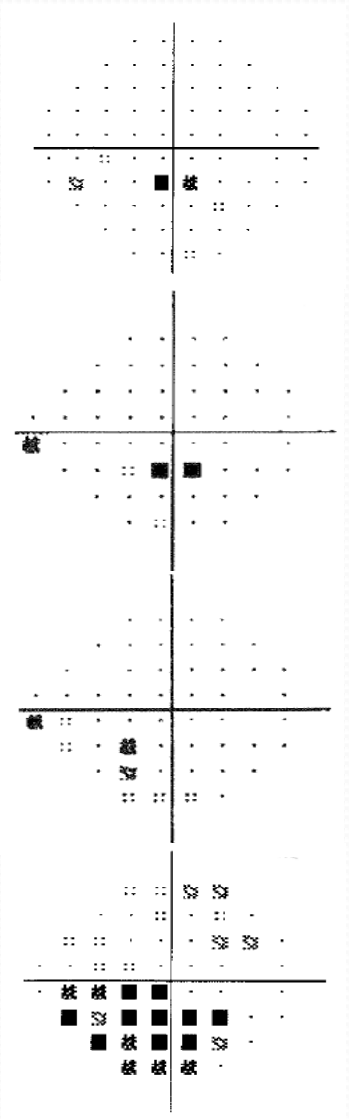
Conclusion/Recommendation

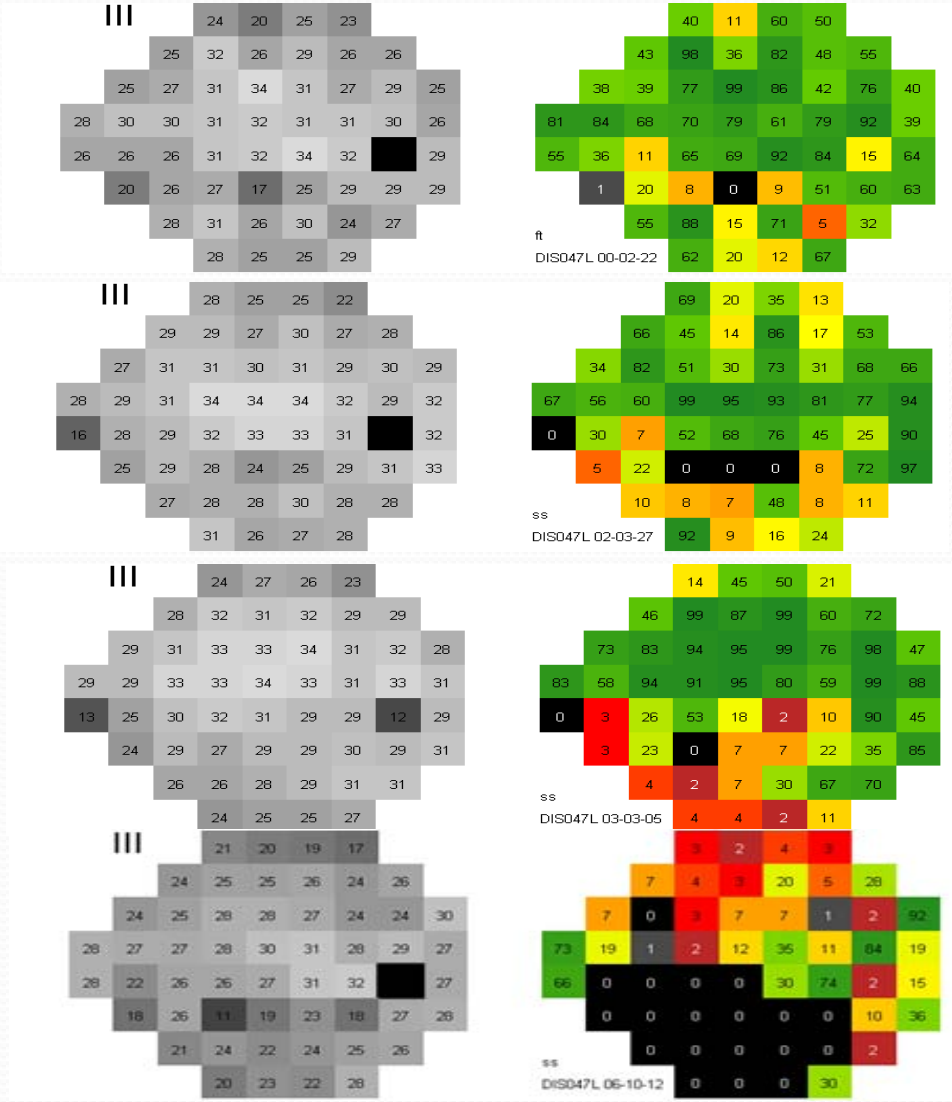
- Note that our glaucoma population has been severely damaged at baseline
- All three methods have signaled a change/progression at the third visit after baseline in more than half of this cohort
- For this group the 3 GCP rank as follow:

Rank	GCP Method
1	GCP(2x4)
2	GCP(8,2x4)
3	GCP(3x4)

- Our recommendation is 2x4 and 8, 2x4

Future Work




III
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25 32 26 29 26 26
25 27 31 34 31 27 29 25
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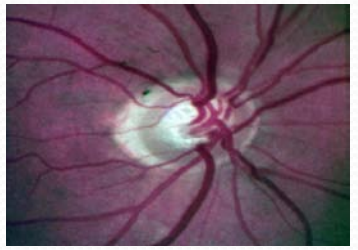
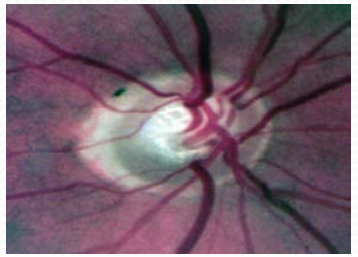
26 26 26 31 32 34 32 29
20 26 27 17 25 29 29 29
28 31 26 30 24 27
28 25 25 29
40 11 60 50
43 98 36 82 48 55
38 39 77 99 86 42 76 40
81 84 68 70 79 61 79 92 39
55 36 11 65 69 92 84 15 64
1 20 8 0 9 51 60 63
55 88 15 71 5 32
ft
DIS047L 00-02-22 62 20 12 67
III
28 25 25 22
29 29 27 30 27 28
27 31 31 30 31 29 30 29
28 29 31 34 34 34 32 29 32
16 28 29 32 33 33 31 32
25 29 28 24 25 29 31 33
27 28 28 30 28 28
31 26 27 28
69 20 35 13
66 45 14 86 17 53
34 82 51 30 73 31 68 66
67 56 60 99 95 93 81 77 94
0 30 7 52 68 76 45 25 90
5 22 0 0 0 8 72 97
10 8 7 48 8 11
ss
DIS047L 02-03-27 92 9 16 24
III
24 27 26 23
28 32 31 32 29 29
29 31 33 33 34 31 32 28
29 29 33 33 34 33 31 33 31
13 25 30 32 31 29 29 12 29
24 29 27 29 29 30 29 31
26 26 28 29 31 31
24 25 25 27
14 45 50 21
46 99 87 99 60 72
73 83 94 95 99 76 98 47
83 58 94 91 95 80 59 99 88
0 3 26 53 18 2 10 90 45
3 23 0 7 7 22 35 85
4 2 7 30 67 70
ss
DIS047L 03-03-05 4 4 2 11
III
21 20 19 17
24 25 25 26 24 26
24 25 28 28 27 24 24 30
28 27 27 28 30 31 28 29 27
28 22 26 26 27 31 32 27
18 26 11 19 23 18 27 28
21 24 22 24 25 26
20 23 22 28
3 2 4 3
7 4 3 20 5 28
7 0 3 7 7 1 2 92
73 19 1 2 12 36 11 84 19
66 0 0 0 0 30 74 2 15
0 0 0 0 0 0 10 36
0 0 0 0 0 2
ss
DIS047L 06-10-12 0 0 0 30

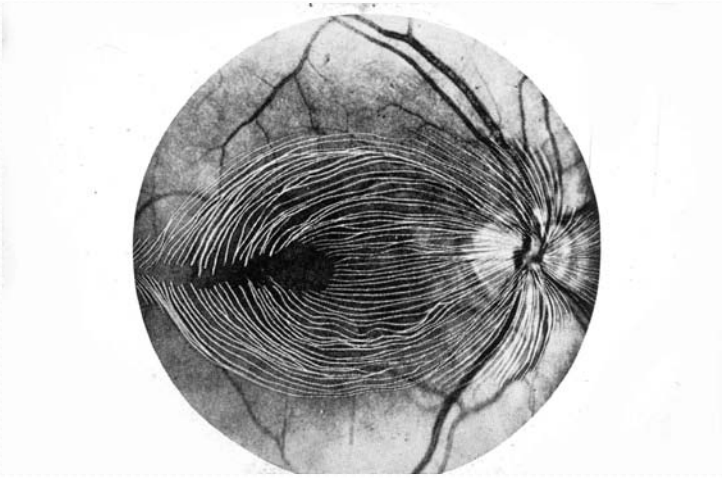


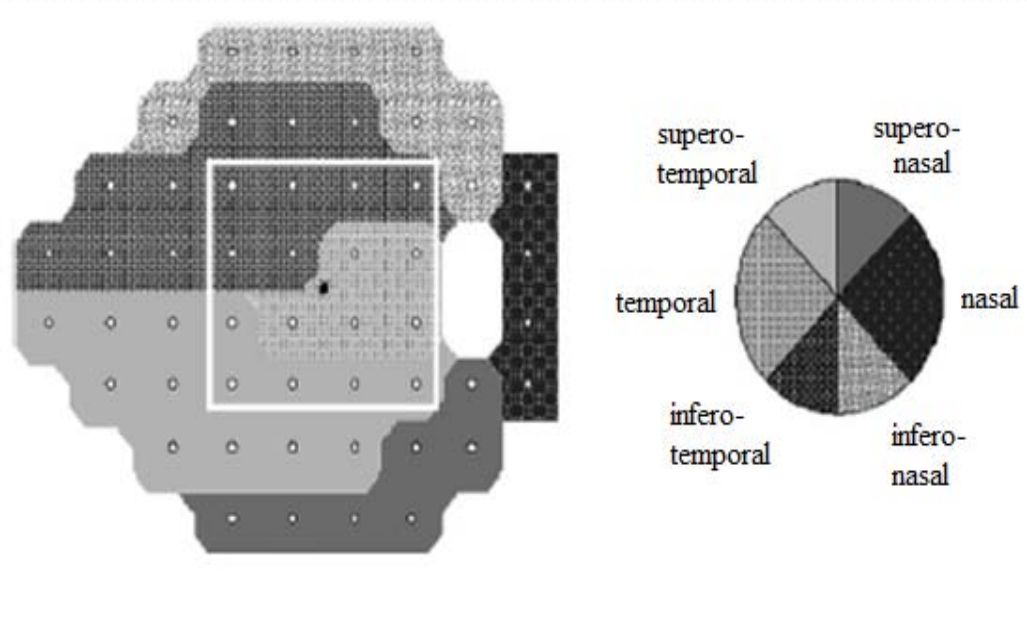


Future Work

Progression seems to occur according to the nerve fiber bundle zones

Temporal, supero-temporal, infero-temporal, nasal, supero-nasal, infero-nasal





Future work

- Model Temporal-Spatial structure to define a bundle zone specific threshold
- Cluster analysis may reduce variability
  - Re-defining the time-indexed glaucoma change probability in a cluster specific way

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Thank you!

Any questions?