



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

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- 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 blindness³.





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 vision¹.



Perimetry Test (Quantification of VF)





Perimetry Test (Quantification of VF)





Single Field Analysis	PRE-LAUNCH EVALUATION SOFTWARE.	Eye: Right
Name: Z CARDONA, GLORIELL		DOB: 09-13-1987
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 Pupil Diameter: 7.5 mm Background: 31.5 ASB Visual Acuity: Strategy: SITA-Fast RX: DS DC X	Date: 07-20-2010 Time: 9:23 AM Age: 22
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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.



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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90 45







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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







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 \le t(result[,-c(26,35)])
 prog.2by4 <- o
 prog.3by4 <- o
 prog.8_2by4 <- 0
 for(i in 1:7) {
  P \le data.frame(unname(N[, i:(i + 2)]))
   v \leftarrow rowSums(subset(P, X_1 == 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, spec.8_2x4, spec.8_2x4))</pre>
```

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", "spec.3x4", "spec.3x4", "spec.8_2x4", "spec.8_2x4")</pre>
```

```
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



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 (9th 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



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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?