IDENTIFYING A USEFUL DYNAMIC RANGE FOR PERIMETRY DATA RELATING TO DISEASE PROGRESSION IN GLAUCOMA PATIENTS

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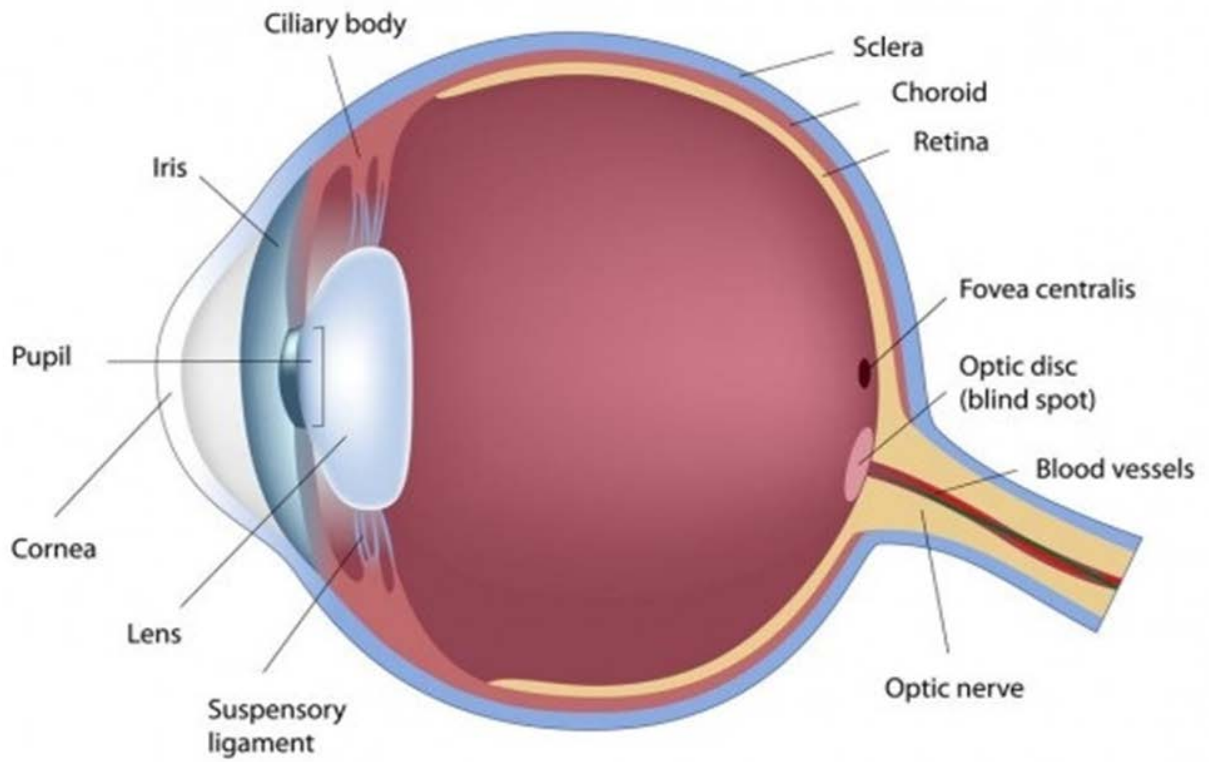
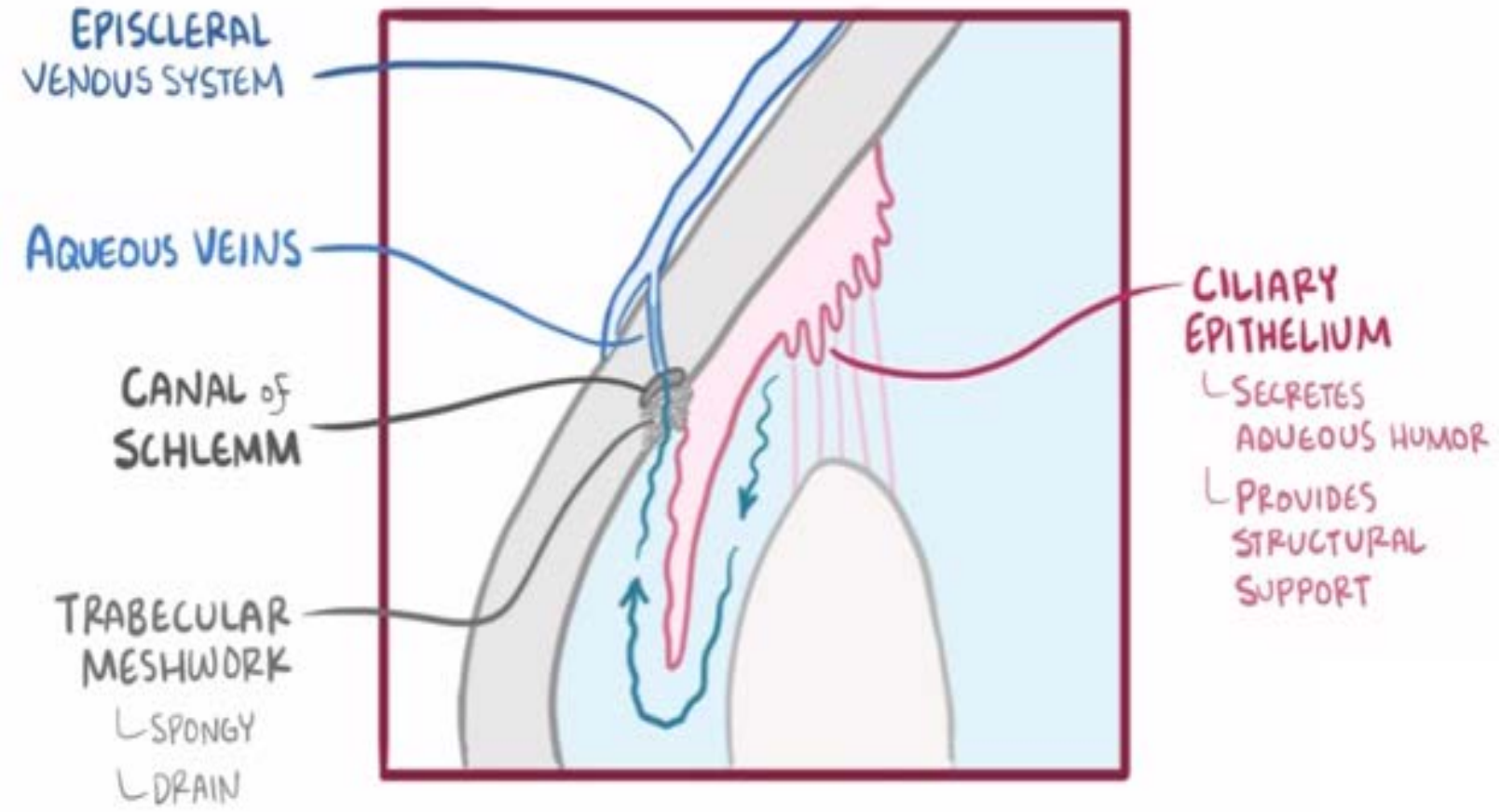
MOTIVATION FOR RESEARCH

- Glaucoma is the 2nd most common cause of **preventable** blindness in the world
- Symptoms can be managed more effectively if disease progression is known
- Tracking the disease accurately is essential
  - Current testing methods struggle to measure progression
  - Our research aims to improve the reliability of testing methods

EYE ANATOMY


Ciliary body
Sclera
Choroid
Retina
Iris
Fovea centralis
Pupil
Optic disc
(blind spot)
Blood vessels
Cornea
Lens
Suspensory
ligament
Optic nerve

WHAT IS GLAUCOMA?

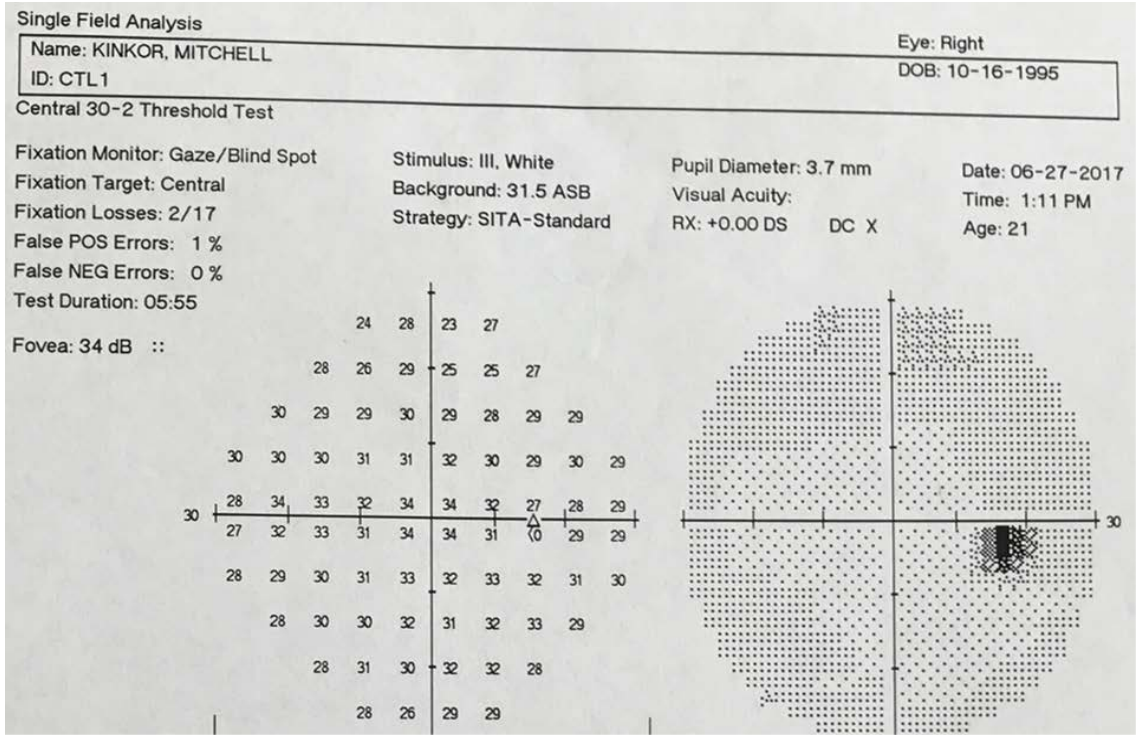


DATA OVERVIEW

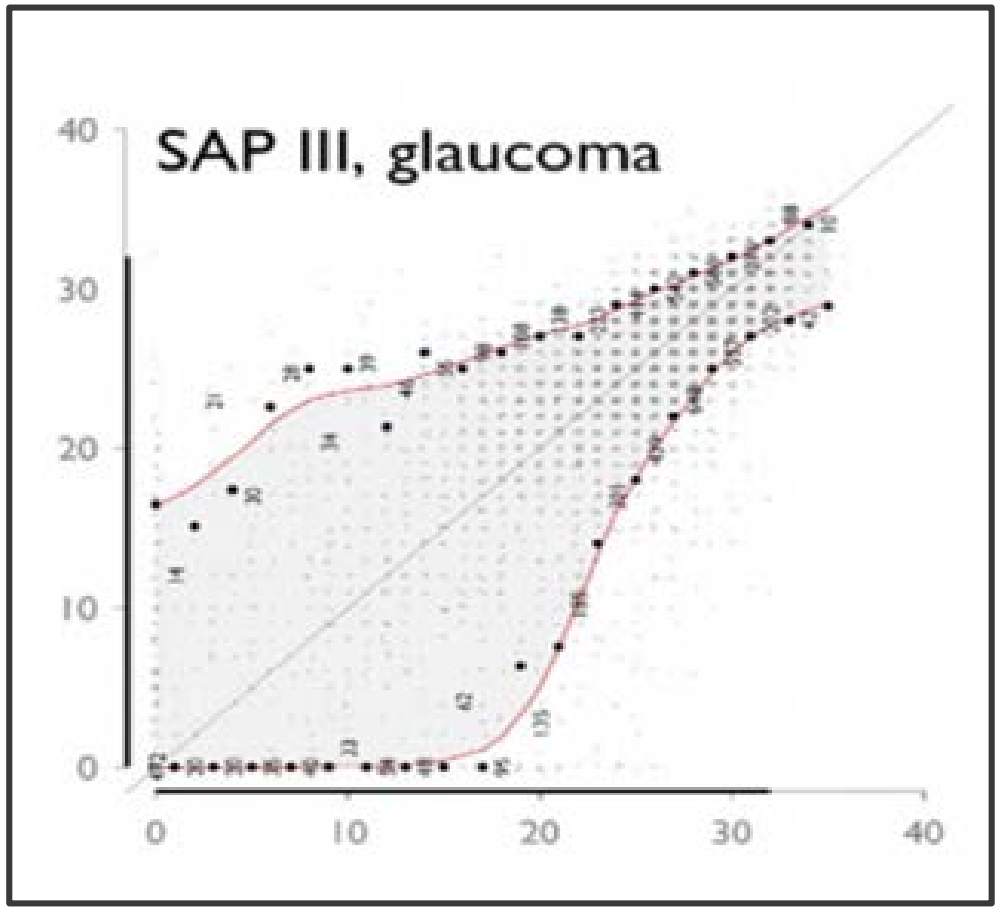
- Perimetry data collected from 120 glaucoma patients over a 4 year period through Iowa Variability in Perimetry Study (IVPS)
- Patients tested 10 times
  - Each patient produces a 10x54 matrix of standard automated perimetry data

STANDARD AUTOMATED PERIMETRY

- Used to map the sensitivity of the visual field in 54 different locations
  - Mechanism of test
  - The smallest stimulus that the patient responds to in each location is known as that location's visual threshold
  - dB scale
    - A higher dB value indicates a lower intensity of light



PROBLEM WITH STANDARD AUTOMATED PERIMETRY



GOALS OF OUR STUDY

1. Find the percentage of glaucoma patients in the IVPS that are significantly progressing according to standard automated perimetry data
   - Compare that percentage to clinical observations

2. Identify a Useful Dynamic Range of dB values for standard automated perimetry data
   - Reproducible values that are reliable for clinicians to use to make medical judgements

STUDY OVERVIEW

Identify location specific progression criterion for 54 different locations in the eye (Linear Regression)

Aggregate location specific criteria to find an eye level criterion (Fisher or Truncated Product Method)

Identify the percent of patients that are showing progression (TPM Distributions)

Left-censor the data and identify the Useful Dynamic Range of dB values (Confidence Interval Analysis)

LINEAR REGRESSION

- Used to determine a p-value for every location of each patient's visual field
- 52 p-values per patient (54 visual field locations-2 blind spots)
  - $H_o: \beta_1 = 0$
    - The patient's glaucoma is not progressing at a specific location of the visual field
  - $H_a: \beta_1 < 0$
    - The patient's glaucoma is progressing because they are gradually responding only to lower dB levels (higher intensities) of light

FISHER'S METHOD

- Properly analyzes multiple hypothesis tests at one time by combining several p-values into one meta-analysis
- Still able to maintain control of the overall alpha level
- Fisher Test Statistic
  - Assumes independence
  - Follows Chi-Square distribution
    - 2*L* degrees of freedom
- A significant Fisher value indicates that a patient's glaucoma is progressing

$$t = -2\sum_{i=1}^{L} \ln p_i$$

t = Fisher test statistic

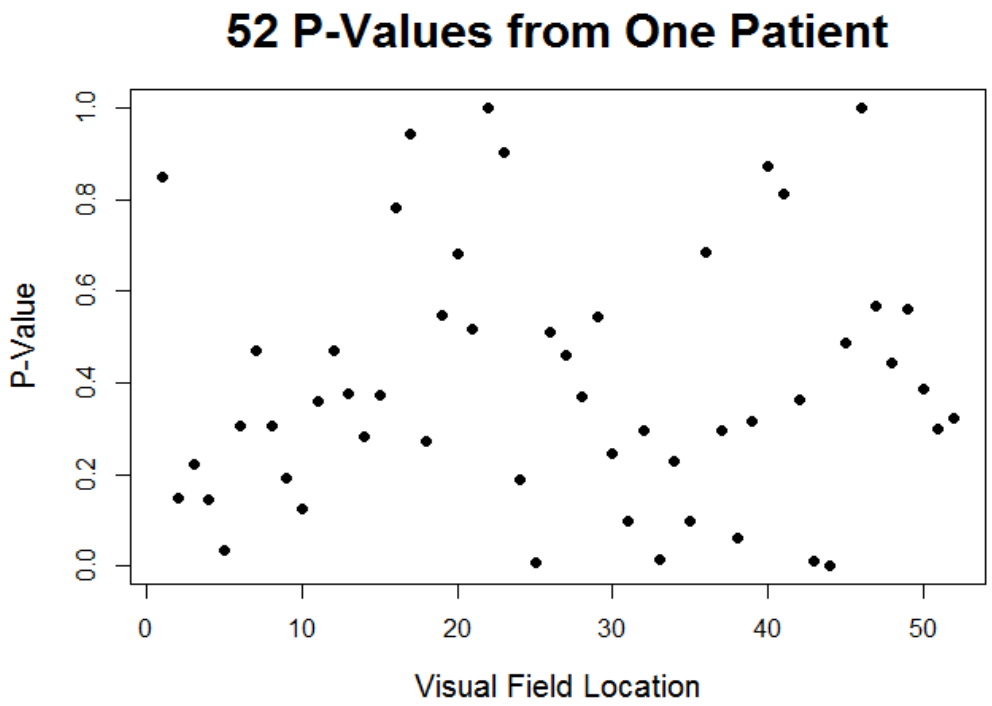
L = number of hypothesis tests

p_i = the probability value

PROBLEMS WITH FISHER'S METHOD

- Fisher's method is not robust to outliers and will lose power with the presence of a few large p-values
  - Patients with early stage glaucoma are not impacted in every location of their visual field
  - They could have multiple large p-values that would mask progression detection

$$t = -2\sum_{i=1}^{L} \ln p_i$$



TRUNCATED PRODUCT METHOD

- Eliminates p-values above a certain threshold that would decrease the power of Fisher's method
  - Problem: The TPM value follows an unknown distribution
    - How do we test the TPM value?
      - We must compute our own distribution

$$W = \prod_{i=1}^{L} p_i^{I(p_i \leq \tau)}$$

W = TPM test statistic

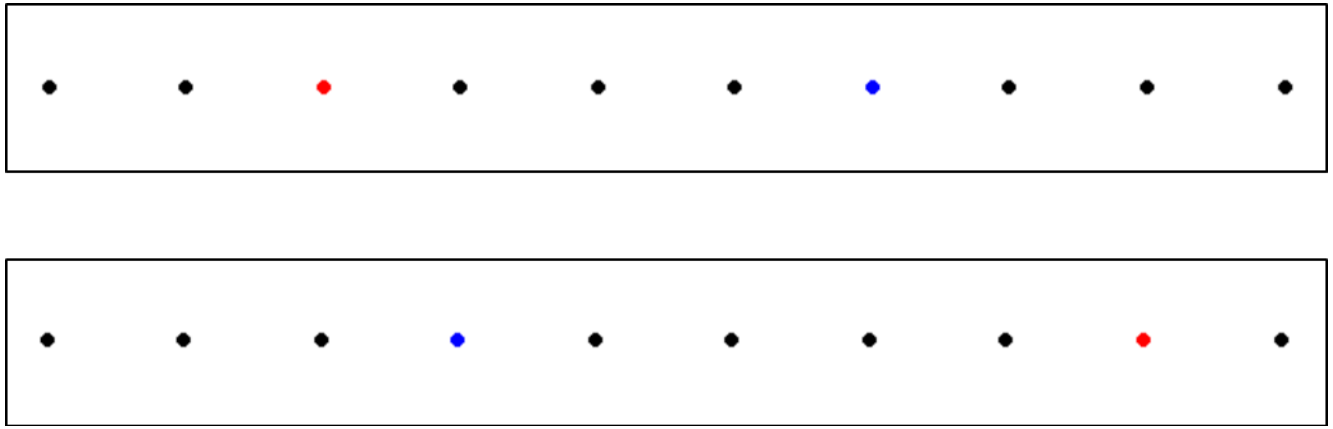
L = number of hypothesis tests

p_i = the probability value

τ = truncation threshold value

COMPUTING TPM DISTRIBUTIONS: PERMUTATION

- To test our TPM test statistic, we must create a TPM distribution for each patient



- If the null hypothesis of no change is true, we should be able to permute the points and obtain the same result.

COMPUTING TPM DISTRIBUTIONS

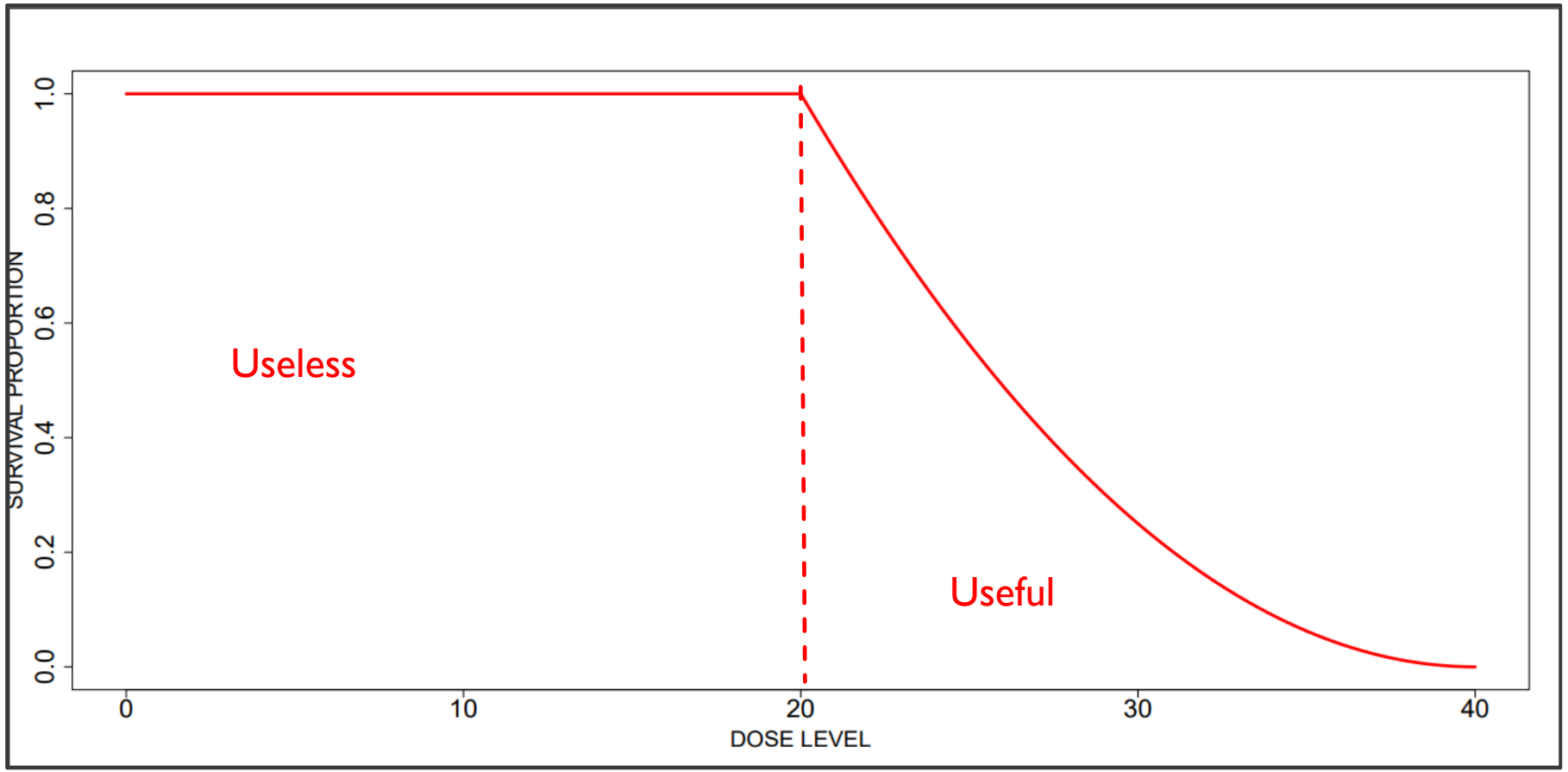
- We permuted the time series 1000 times in every patient
- After each permutation, we computed a new TPM value to create a TPM distribution curve for each patient
- Based on the permuted distribution, we can estimate the chances of finding values that are as extreme/more extreme than the unpermuted test statistic
  - Example: Set α level for test at .05
    - If fewer than 50 of our computed values (α =50/1000) are greater than our initial TPM value, we know that our initial TPM value is significant and the patient's glaucoma is progressing

RESULTS OF TPM DISTRIBUTIONS

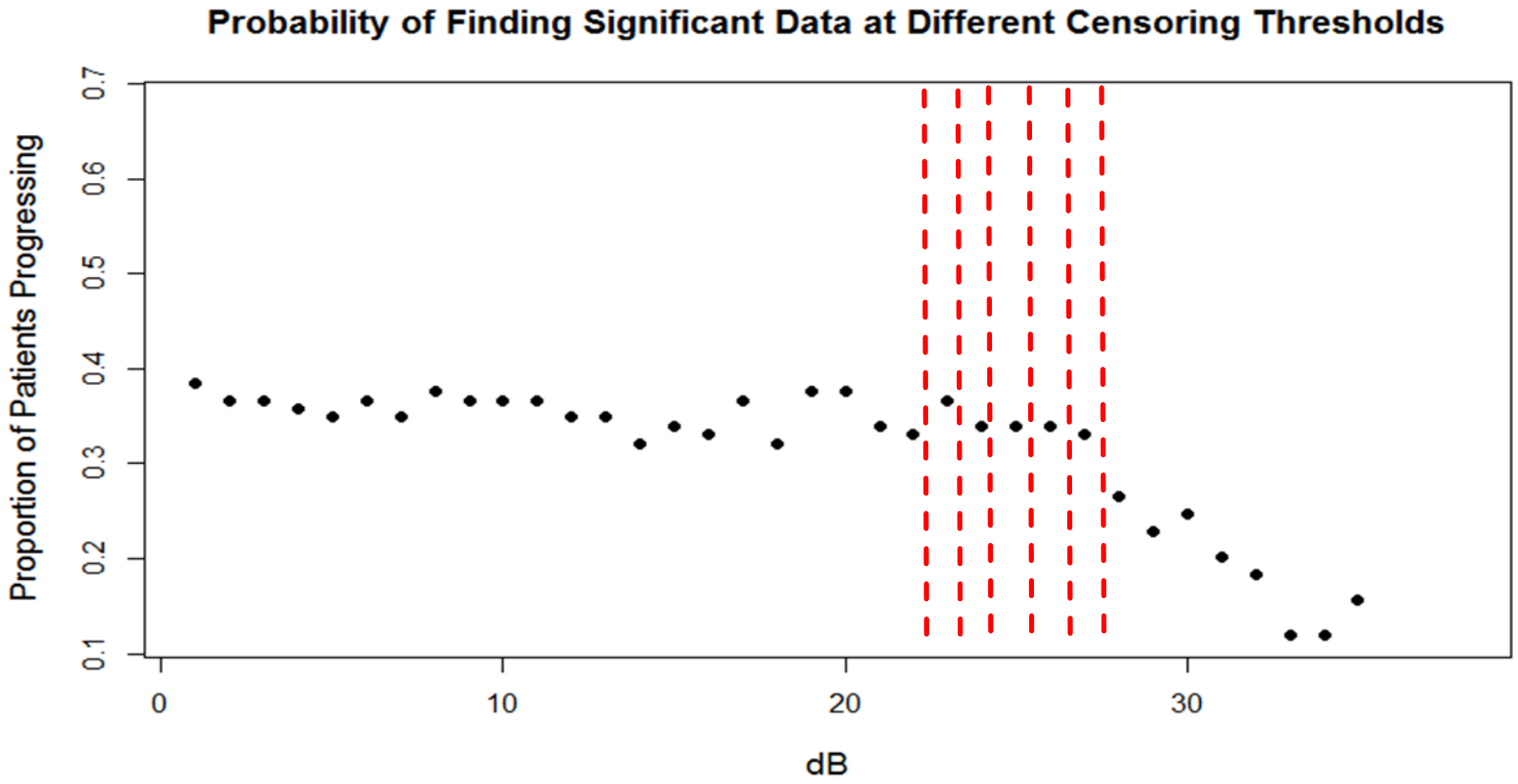
- When τ = .01 and α = .05, the TPM distributions indicated that 38.5% of the patients in our study had glaucoma that was significantly progressing
- Ophthalmologists conducting the study believed around 25-40% of the glaucoma patients to be progressing
  - Statistical results aligned with clinical observations.

- Next problem
  - We still do not know which decibel levels are part of the Useful Dynamic Range

CENSORING THE DATA: PESTICIDE IN A CORN FIELD



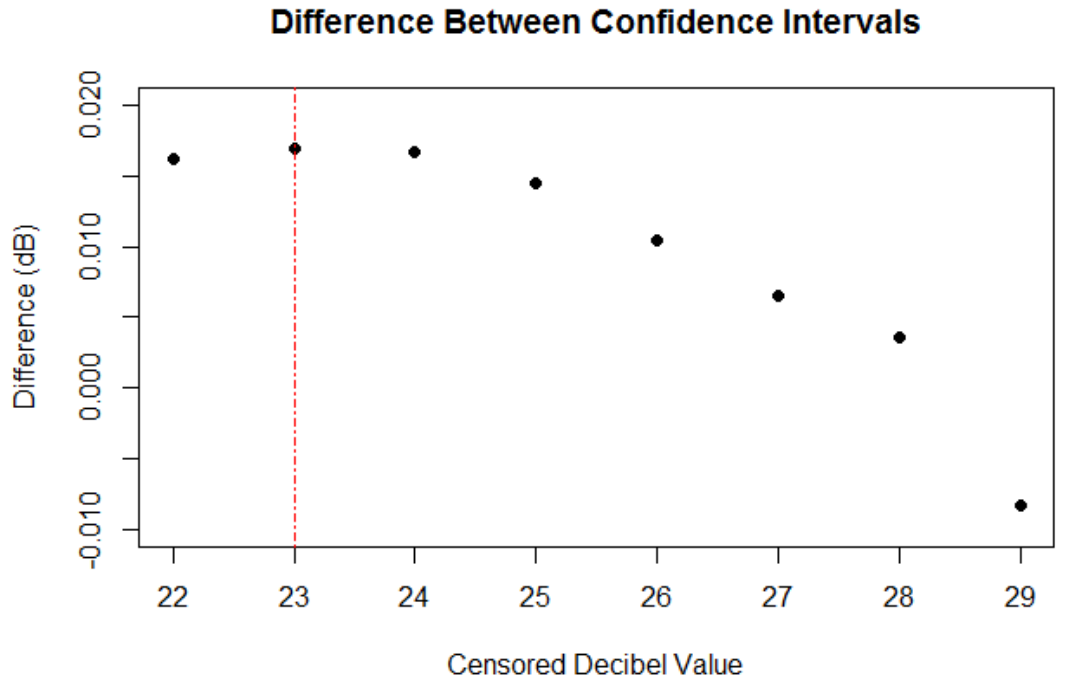
RESULTS



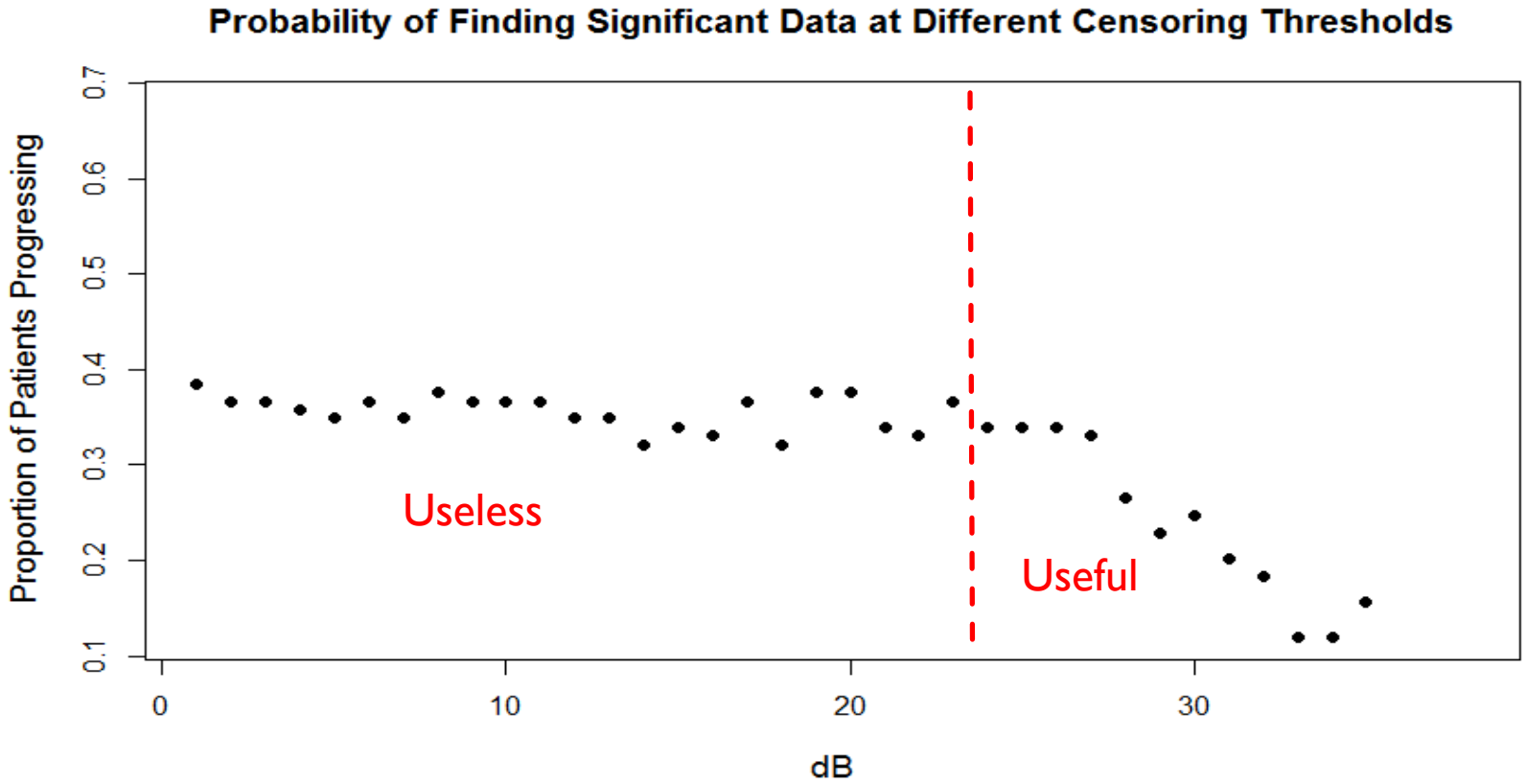
Where is the breakpoint?

RESULTS: FINDING THE BREAKPOINT

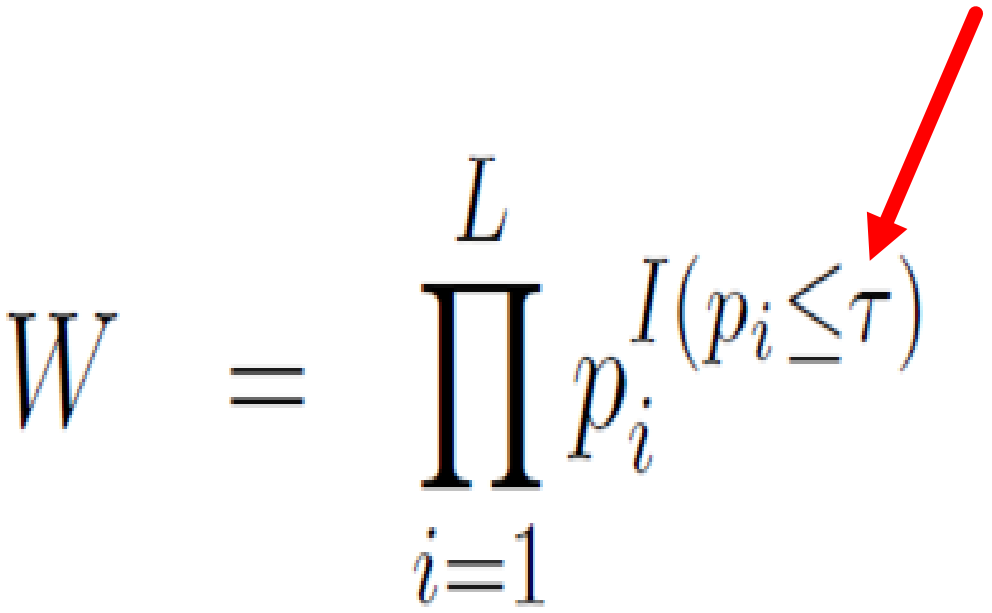
- Identify potential break points via eye test
- Took the slope of the line before the tested break point and the line after the break point
- Found confidence intervals for the slope of both lines
- Break point = point with the maximum gap between the confidence intervals of the slopes



RESULTS



The most significant difference between the confidence intervals of the slopes was between the regression line of the 0-23dB values to the regression line of the 24-35dB values.



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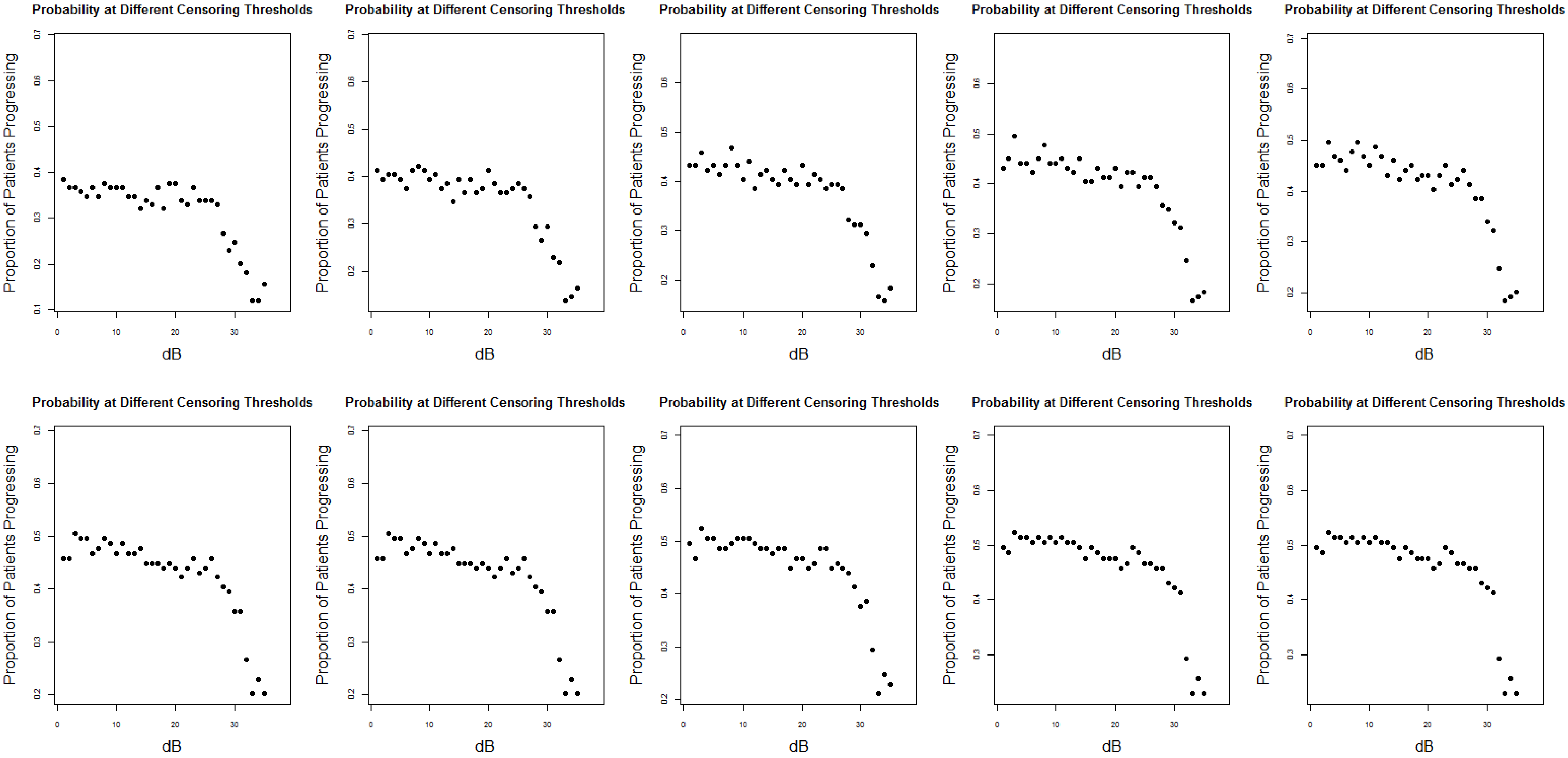
Probability at Different Censoring Thresholds
Proportion of Patients Progressing
dB
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dB

FURTHER RESEARCH POTENTIAL

- Validate the model with simulations
- Incorporate variables besides SAP data
- Factor in the correlation between different visual field areas
- Change size of SAP stimuli to potentially generate more reproducible data

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REFERENCES

- AirDrie. (2016). Eye Health: Anatomy. Retrieved from http://www.airdriefamilyeyedoctors.com/anatomy.php
- Davis, C., Zamba, K. D., Doyle, C. K., Sherman, K., Johnson, C., Wall, M. (May 2011). Bigger is better: Larger stimulus sizes reduce test-retest variability in visual field testing of glaucoma patients. Poster presentation, ARVO 2011, Fort Lauderdale, Florida.
- Osmosis. (2016). *Glaucoma (open-angle, closed-angle, and normal-tension) - pathology, diagnosis, treatment.* Retrieved from https://www.youtube.com/watch?v=f-tva2zj0H0
- Sahri, N., (2016). *Overview of Primary Open Angle Glaucoma.* Retrieved from https://homenworkoptometrycare.wordpress.com/2016/10/11/overview-of-primary-open-angle-glaucoma/
- Zaykin, D., etal. (2002). Truncated Product Method for Combining *p*-values. *Genet Epidemiol.* 22(2): 170-85