Cohort Studies

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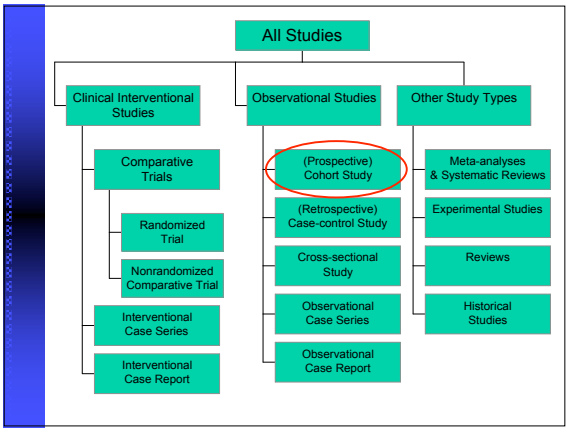


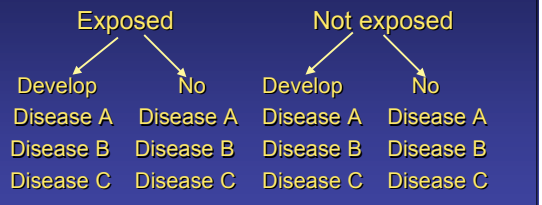
Definition of Cohort Study

(Also known as longitudinal, follow-up, or prospective study)

- Follow-up of exposed and non-exposed defined groups, with a comparison of disease rates during the time covered.

Design of a Cohort Study

Design of a Cohort Study
(Can study multiple diseases)



Two types of Cohort Studies

Cohort Study

Advantages
- Incidence rates can be calculated
- Precise exposure measurement possible
- Temporal relationship between exposure and disease easily established
- Many disease outcomes studied simultaneously
- Possible to study multiple exposures when population selected on factor unrelated to exposure

Limitations
- Expensive
- Long duration
- Large sample needed
- Not optimal for rare disease
- Selection of non-exposed comparison group often difficult
- Loss to follow-up

Framingham Study
Early cohort study

- Possible to study multiple exposures when population selected on factor unrelated to exposure
- Studied many exposures such as weight, blood pressure, smoking, cholesterol levels and physical activity

Definition of Case-Control Study
(Also known as retrospective study)

- Retrospective comparison of exposures of persons with disease (cases) with those of persons without the disease (controls).

Case Control Studies

Exposed Not Exposed Exposed Not Exposed

Disease No Disease

Case-Control Study

Advantages

- Relatively inexpensive
- Shorter duration
- Desirable when disease occurrence is rare
- Many exposures studied simultaneously

Limitations

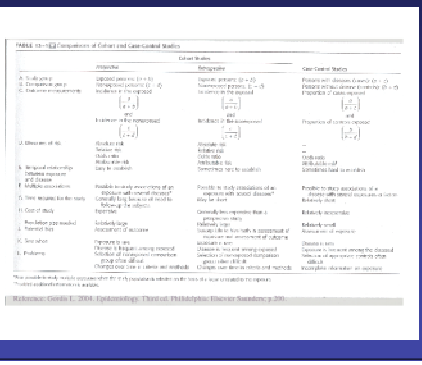
- Incidence rates cannot be calculated
- Relative risk cannot be calculated (estimated with odds ratios)
- Bias in exposure measurement possible (recall bias)
- Temporal relationship between exposure and disease not easily established
- Not optimal for rare exposures
- Selection of non-diseased comparison group often difficult

Case Control Study

Cohort Study

	Disease	No Disease
Exposed	a	b
Not Exposed	c	d

See handout



Diagnostic Innovations DIGS in Glaucoma Study

Principal Investigators:

•Pamela Sample:	Visual Function	NIH EY08208
•Linda Zangwill:	Structural Assessment	NIH EY11008

DIGS Co-Investigators:

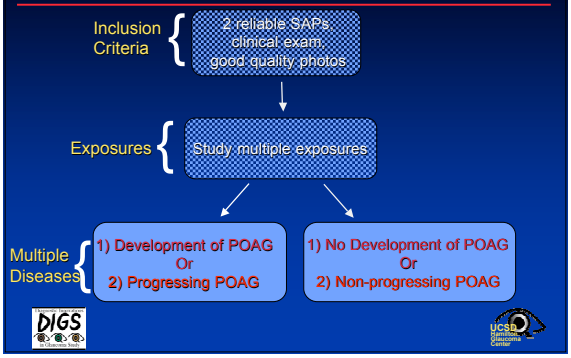
Robert Weinreb, M.D.
Christopher Bowd, Ph.D.
Catherine Boden, Ph.D.
Felipe Medieros, M.D.
Charles C. Berry, Ph.D.

DIGS Objectives:

To Characterize

- **Structural and Functional Damage and Progression in Glaucoma**
- **Rates and Patterns of Progressive Glaucomatous Damage**

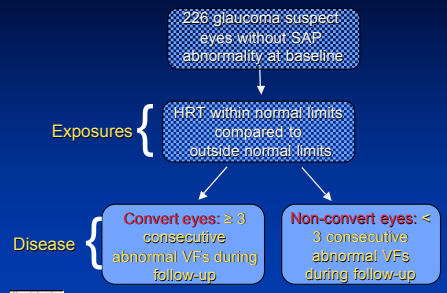
DIGS
(Diagnostic Innovations in Glaucoma Study)



DIGS

- **Most publications to date have been cross-sectional**
- **Need long duration for sufficient number of endpoints**

DIGS
Examples of published cohort analyses



Bowd, Zangwill, Medieros et. al IOVS 2004

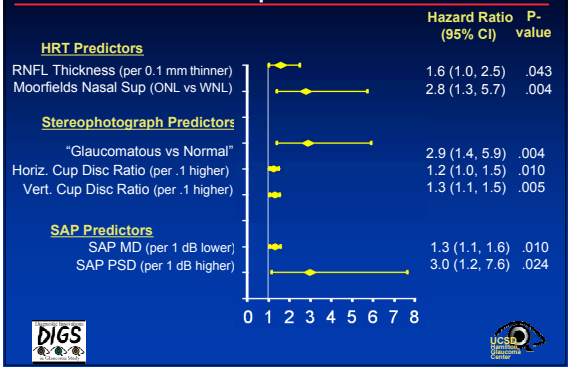
226 Subjects Met Inclusion Criteria:

- Age ≥ 40 years
- Minimum follow-up of 2 years (mean: 4 years)
- Good quality baseline HRT image and photograph
- Normal standard automated perimetry (SAP) results at baseline HRT (CPSD and GHT within normal limits)
- Optic disc appearance was not used to determine eligibility

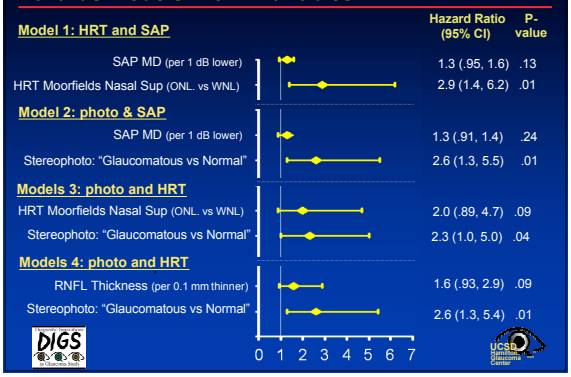
Visual Field Endpoint: Standard Automated Perimetry (SAP)

- 37 eyes converted to glaucomatous SAP VF
  - ≥ 3 consecutive, reliable, "glaucomatous" SAP VF, based on CPSD / PSD and / or GHT outside normal limits
- 189 eyes did not convert to glaucomatous SAP VF
  - < 3 consecutive SAP VF outside normal limits

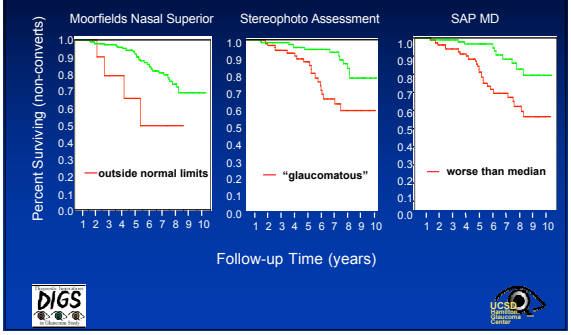
Significant Baseline Predictive Factors from Univariate Proportional Hazards Models



There were several similar Multivariate Proportional Hazards Models with 2 variables



Cumulative Survival Curves for Significant Independent Predictors in Multivariate Models



Major Sources of Bias in Cohort Studies

- Bias in ascertainment of outcome: If persons who decides disease status knows exposure status and hypothesis, may have biased judgment
  - Precise assessment (visual fields well characterized)
  - Masked to exposure status
- Information bias: If quality and extent of information obtained is different for exposed and unexposed
  - Did not need to "select" an exposed and unexposed group, came from same source- DIGS population
  - Precise assessment of exposure possible (Imaging, risk factors etc)

Major Sources of Bias in Cohort Studies

- Bias from nonresponse and loss to follow-up: Are those that choose to participate (agree) and remain in study (continue medical care at clinic) different from those who do not?
  - Change in insurance: Established research clinic for those no longer seen in clinic
- Analytic bias: Preconceptions of investigators who are analyzing the data may unintentionally introduce biases into their analyses and interpretation of results
  - Financial disclosure
  - Non-financial investment

Other Methodological Issues

study designed to reduce possible sources of bias

- Source population
  - Not population based
  - May not be representative of general glaucoma population
- Inclusion criteria
  - No optic disc criteria
  - Informally may influence

Methodological issues related to studying diagnostic techniques:
Evidence based medicine recommendations

- Independent gold standard
  - For imaging studies, based on visual field and not optic disc damage
- Gold standard applied similarly regardless of participants' disease status or test result
  - All participants get tested in a similar manner
- Include participants with diagnostic uncertainty
  - Early glaucoma included
  - Are healthy comparison group "super normals?"
- Present data as likelihood ratios

Likelihood ratio

Pre-test probability of glaucoma

IMAGING TEST

How much does the test change the probability of disease?

Post-test probability of glaucoma ?

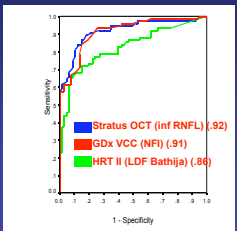
LIKELIHOOD RATIO

$$\frac{\text{Probability of test result in patients WITH disease}}{\text{Probability of test result in patients WITHOUT disease}}$$

- LR = 1 : Test result provides no additional information
- LR > 1 : Test result increases the likelihood of disease
  - LR ≥10 : Large effect
  - 5 ≤ LR <10: Moderate effect
  - 2 ≤ LR < 5: Small effect
  - 1 < LR < 2: Insignificant effect

Comparison of GDx VCC, HRTII and Stratus OCT for the Detection of Glaucoma

Medieros, Zangwill, Bowd & Weinreb Arch Ophthalmol 2004: 122; 821-831



GDX VCC NFI	Likelihood Ratio (95% CI)
0 to 15	.04 (.01 - .30)
25 to 35	2.1 (1.3 - 3.3)
> 35 to 50	4.0 (2.0 - 7.7)
> 50	Infinity

OCT Inf. RNFL	
≤ 70	Infinity
>70 to 90	21.1 (14.0 - 31.8)
>90 to 110	1.8 (1.2 - 2.9)
> 130	.07 (.01 - .28)

HRTII LDF	
≤ -1.0	.08 (.02 - .34)
>0 to 1.0	.9 (.6 - 1.5)
> 1.0 to 2.0	15.8 (9.9 - 25.3)
> 2.0	infinity

Discussion and Thank You