Resources for Reader Studies

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Interesting Quote

- Editors of *Radiology*:
  - The audience of their journal is interested in
  - the variability between observers which
  - "*requires a sufficiently high number of observers*."

Bankier, A. A.; Levine, D.; Halpern, E. F. & Kressel, H. Y. (2010),
'Consensus interpretation in imaging research: is there a better way?'
Radiology, ***257, (1), 14--17.***

Interesting Quote

- American College of Radiology Imaging Network (ACRIN)
  - There is a great deal of variability among readers.
  - Reader variability "*must be accounted for in the design of ACRIN trials*."

Hillman, B. J. (2005),
'ACRIN–lessons learned in conducting multi-center trials of imaging and cancer.'
Cancer Imaging, ***5 Spec No A, S97--101.***

Phases of Evaluation

- Exploratory
  - Early
  - Pilot
- Intermediate
  - Challenge or Stress Test
  - Lab-based
- Advanced
  - Late
  - Clinical use

- Phase determines
  - Aims
  - Scope
  - Size
  - Analysis
  - Conclusions

- See my workshop summary paper in Academic Radiology

Gallas, Chan, D'Orsi, Dodd, Giger, Gur, Krupinski, Metz, Myers, Obuchowski, Sahiner, Toledano, Zuley (2012), 'Evaluating Imaging and Computer-aided Detection and Diagnosis Devices at the FDA.'
Acad Radiol, ***19, (4), 463-477.***

Outline

- Data Collection and Reader Training
- Statistical Analysis and Sizing
- Split-Plot Study Design

Considerations

Data Collection

- Study task is distilled version of clinical task
  - No patient information
  - Limited decision options
  - Quantitative, ready for analysis
- Test and streamline workflow

Reader Training

- Provide Precise Written Instructions
- Discuss Instructions Face-to-Face
- Observe and assist training cases
- Cost is minimal compared to
  - Sourcing images
  - Reading time
  - Total effort

Resources

Data Collection

- eeDAP: Evaluation Environment for Digital and Analog Pathology
  - Retooling: integrate other image formats
  - Does not require images
  - Migrating to cloud platform
  - Can tweak to your needs
  - https://code.google.com/p/eedap/

Reader Training

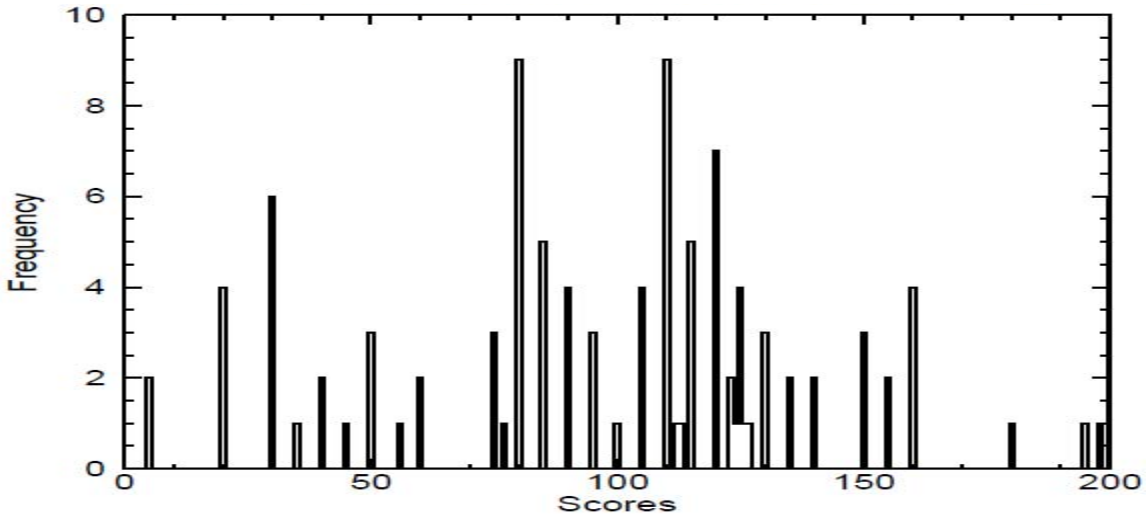
- Instructions for ROC scoring
- Novel ROC data collection workflow (200 point scale)
- iMRMC website
  - https://code.google.com/p/imrmc/wiki/iMRMCGuide

Reader 02, Screening study (prevalence = 0.31)

SFM

nCases = 109

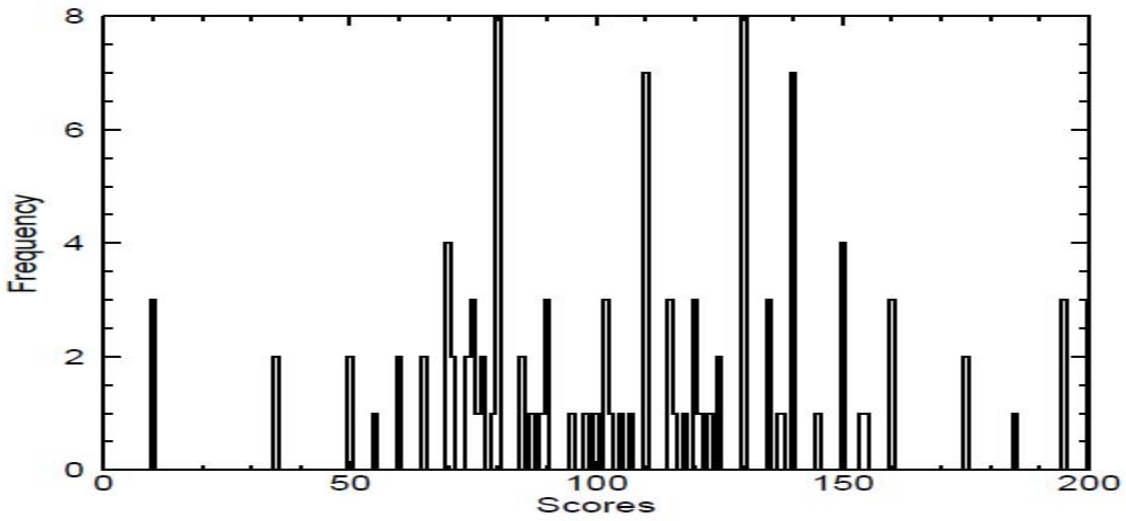
nBinsUsed = 37



FFDM

nCases = 109

nBinsUsed = 47



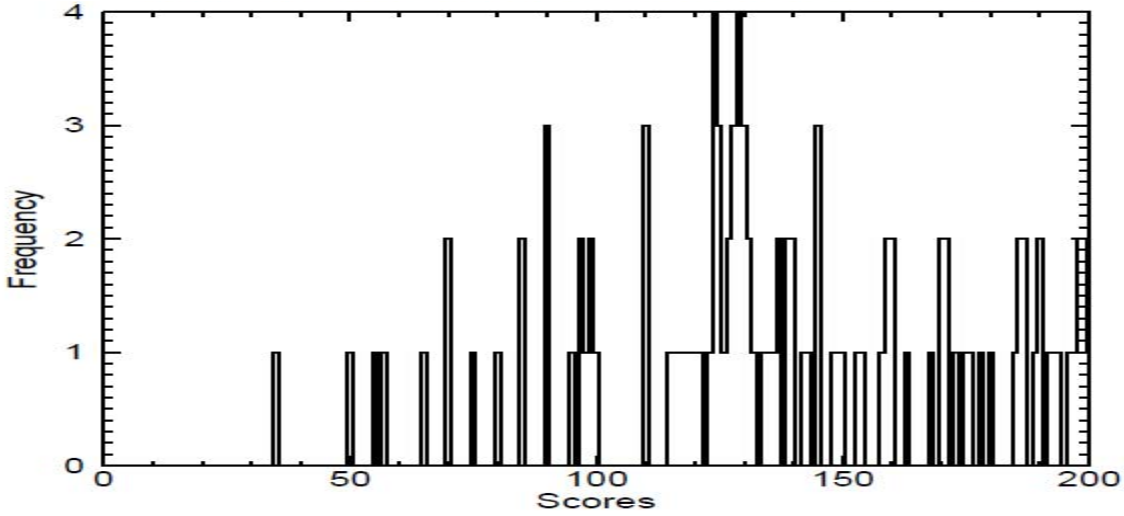
FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation

Reader 03, Screening study (prevalence = 0.31)

SFM

nCases = 108

nBinsUsed = 72



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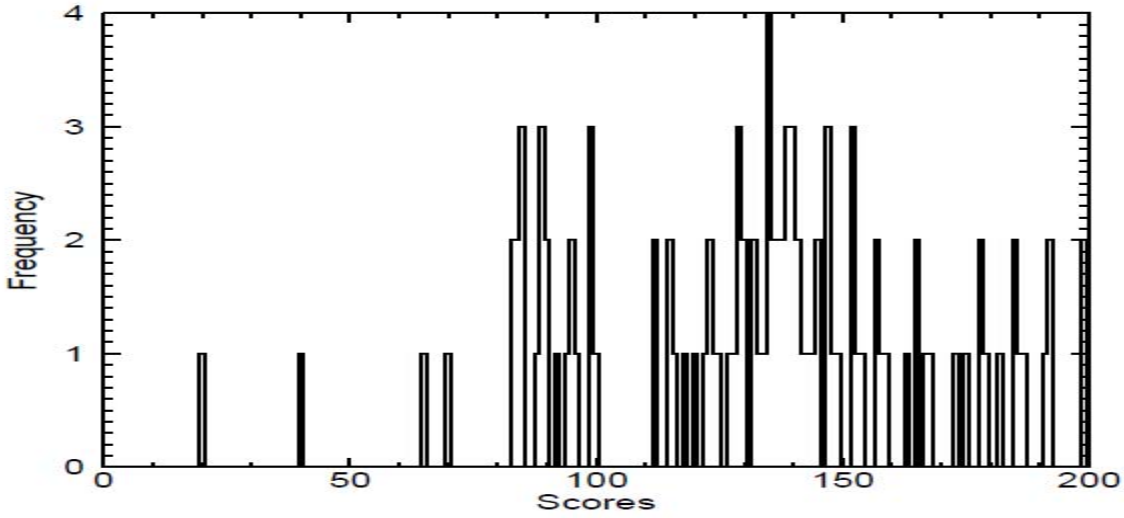
nCases = 106

nBinsUsed = 67



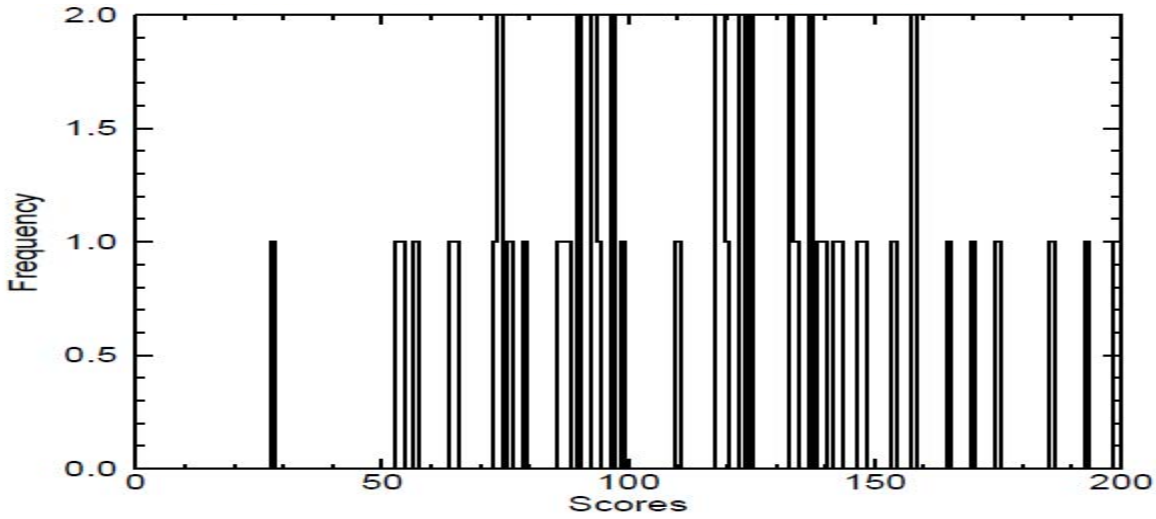
FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation

Reader 04, Screening study (prevalence = 0.31)

SFM

nCases = 53

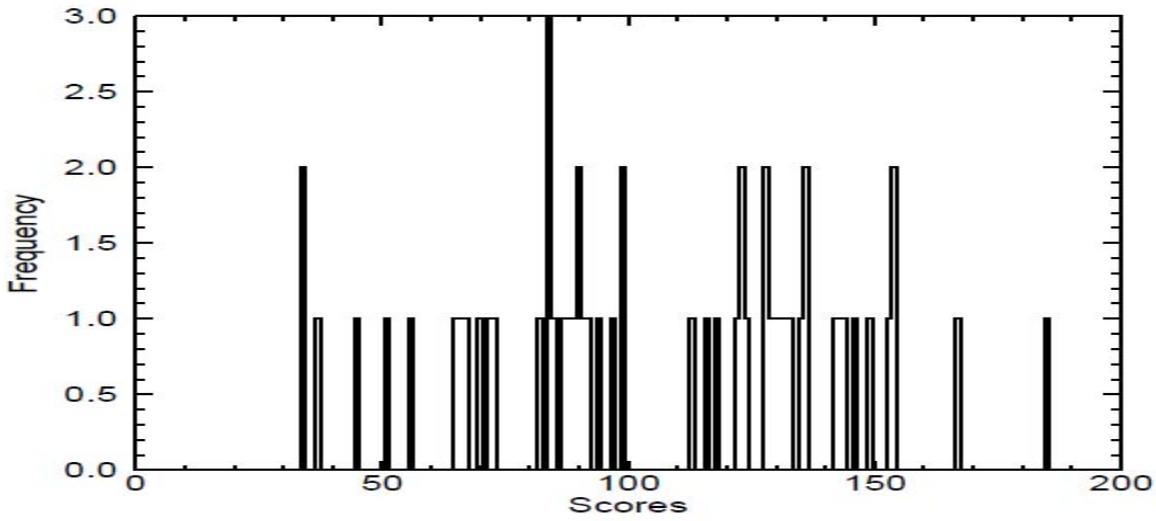
nBinsUsed = 42



FFDM

nCases = 55

nBinsUsed = 46



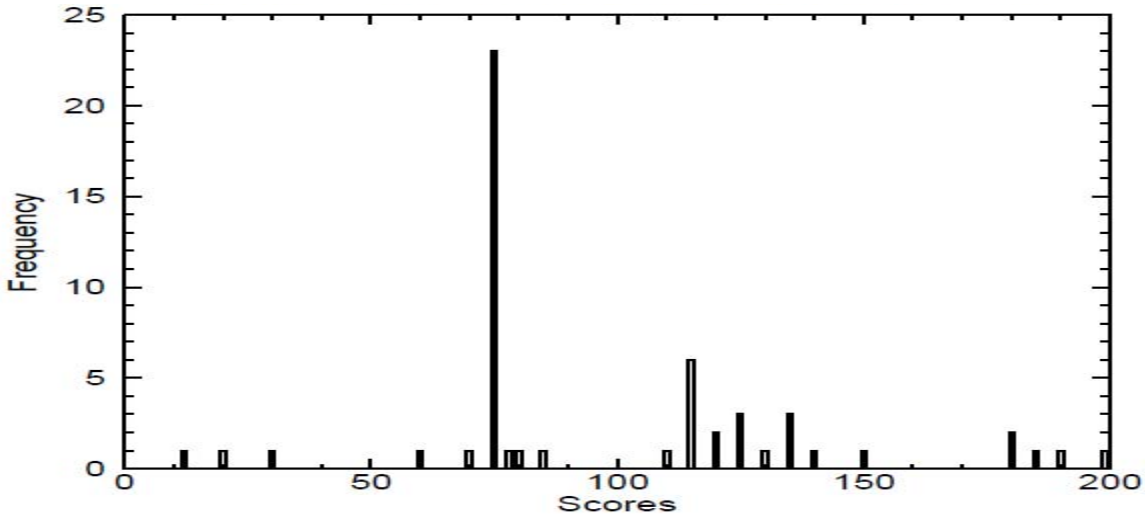
FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation

Reader 01, Screening study (prevalence = 0.31)

SFM

nCases = 54

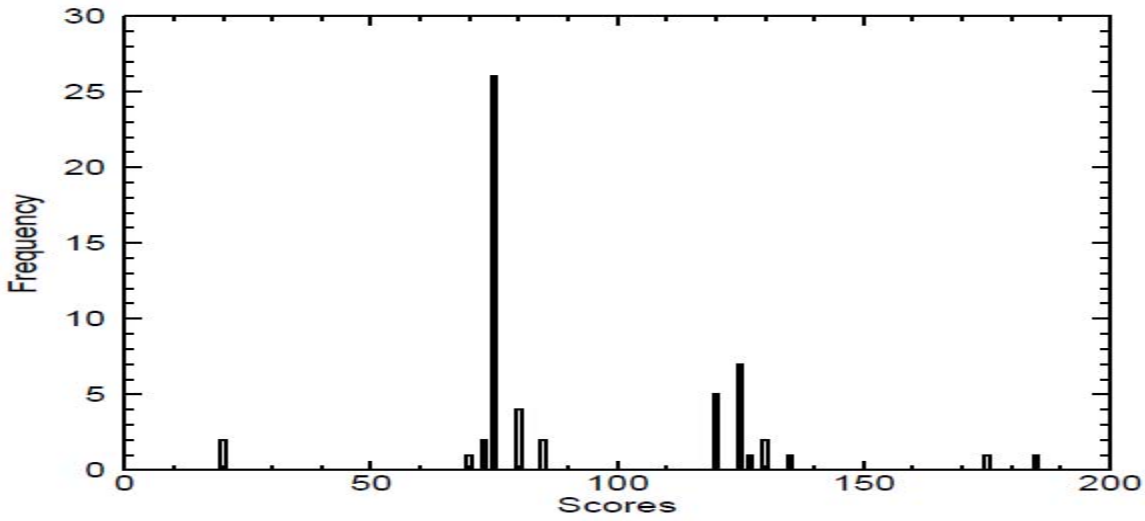
nBinsUsed = 21



FFDM

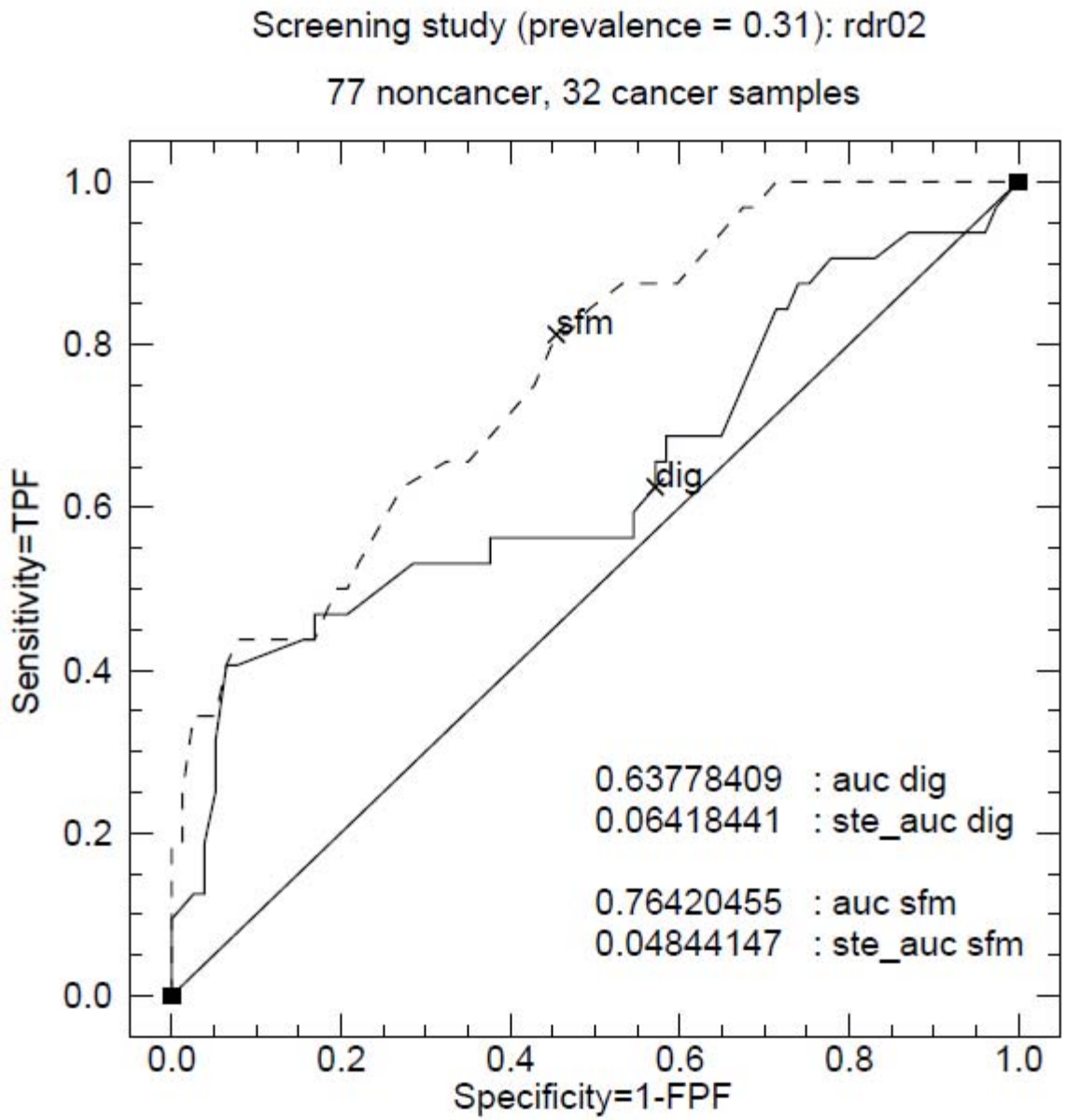
nCases = 55

nBinsUsed = 13



FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation

Goto ROC curves



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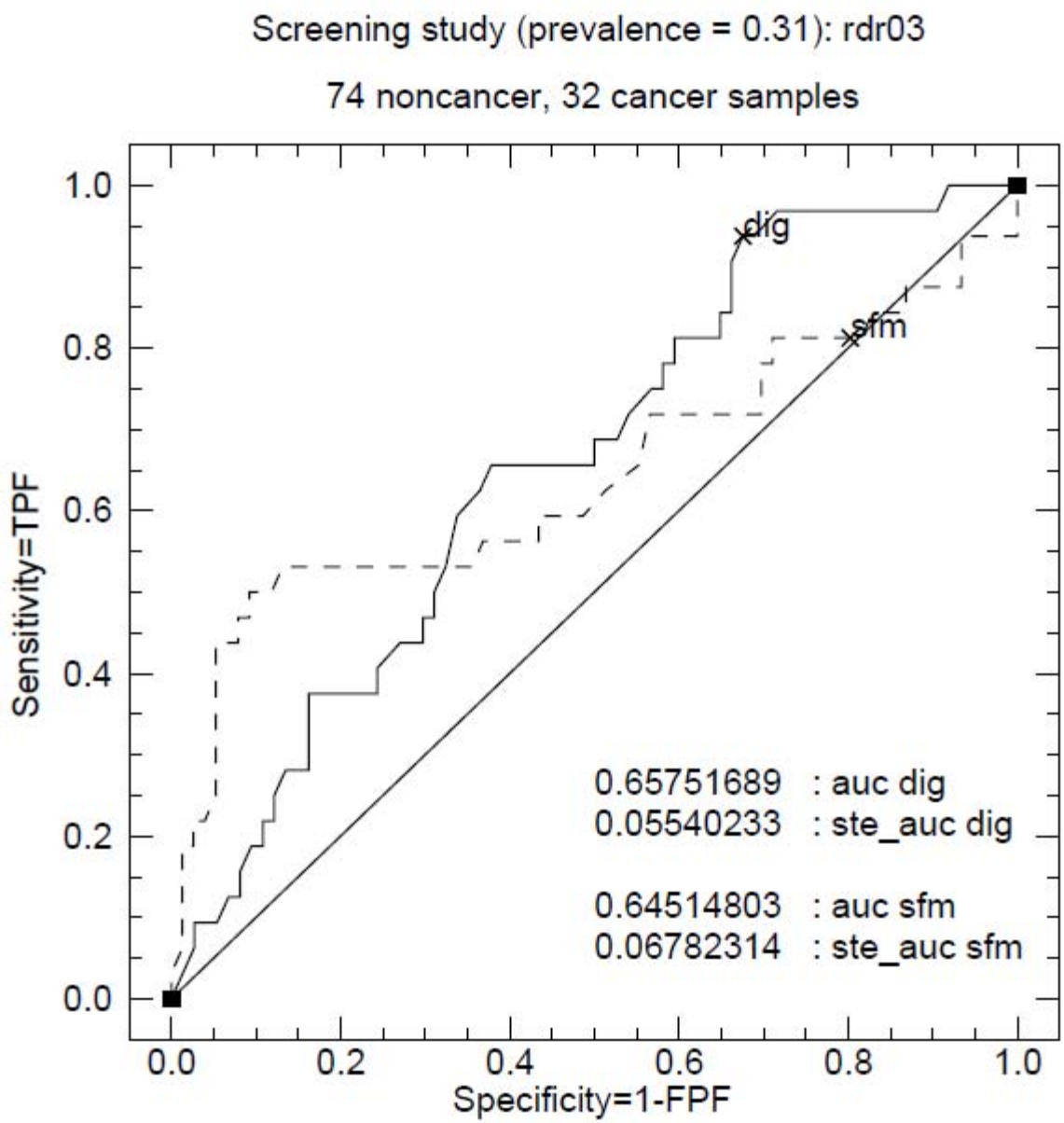
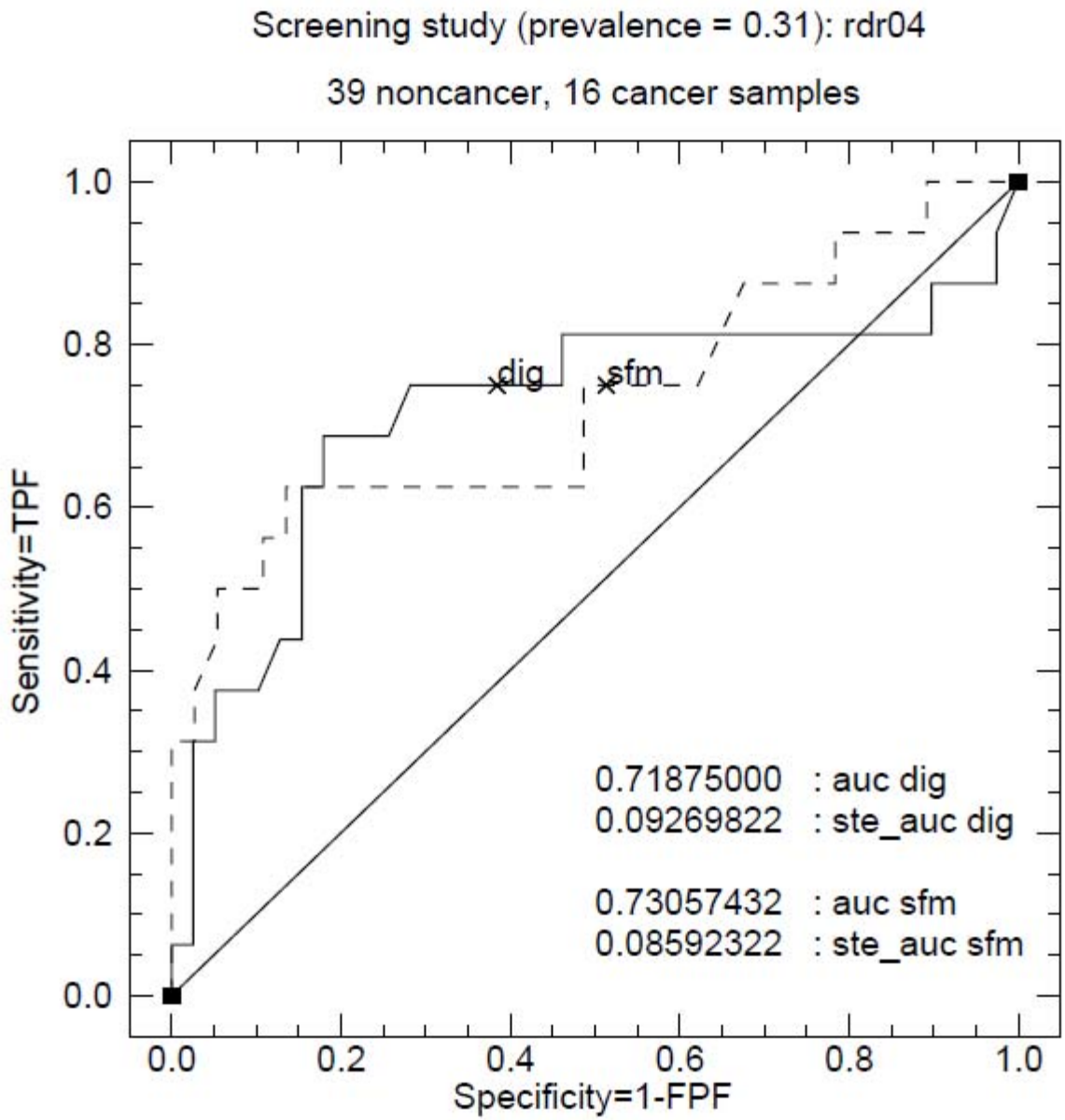
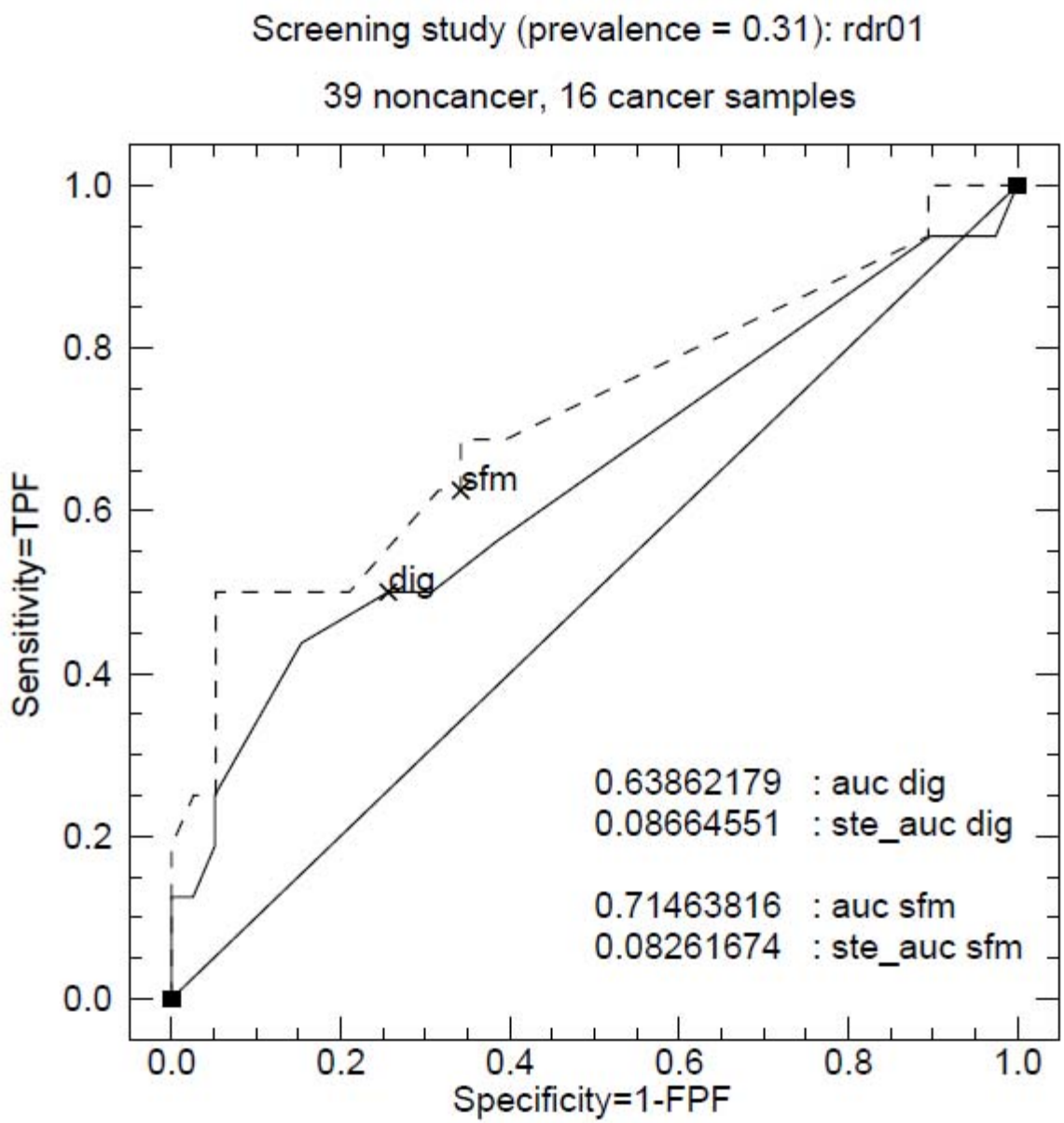


FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation



FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation



FDA VIPER data: Validation of Imaging Premarket Evaluation and Regulation

"MRMC" Statistical Analysis

Accounts for **M**ultiple **R**eaders, **M**ultiple **C**ases

- Components-of-variance

Variance of Difference in Endpoints

$$V = \frac{\sigma_r^2}{R} + \frac{\sigma_c^2}{N} + \frac{\sigma_{rc}^2}{RN}$$

internal noise, reader jitter

reader case reader-case

- Variance estimation is first step for
  - Confidence Intervals
  - Hypothesis Testing

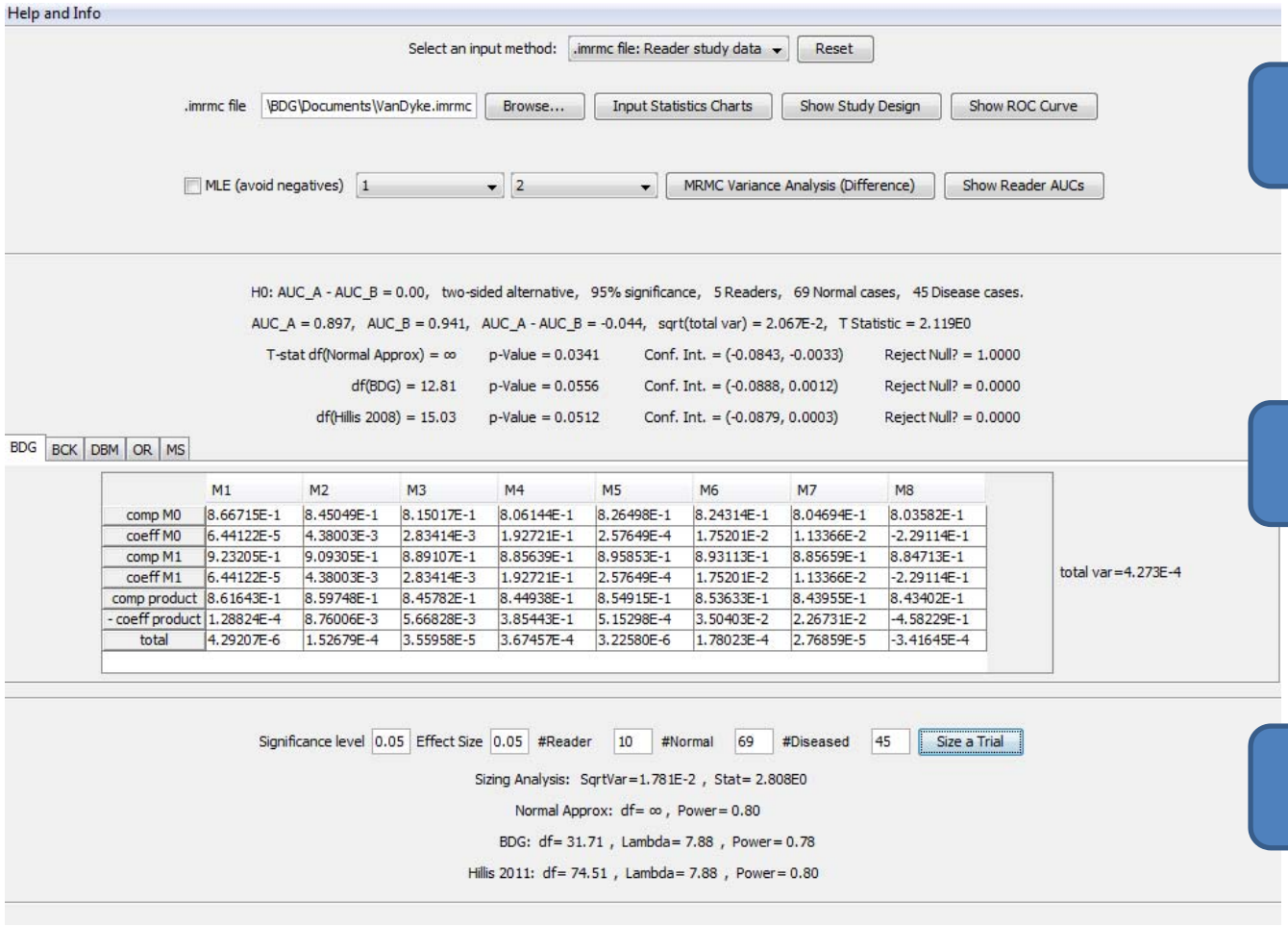
MRMC Statistical Analysis Tools

- University of Chicago
  - http://metz-roc.uchicago.edu/
- University of Iowa
  - http://perception.radiology.uiowa.edu/Home/tabid/87/Default.aspx
- FDA: iMRMC
  - https://code.google.com/p/imrmc/

MRMC Analysis of the Area Under the ROC curve (AUC)
+ Alternate study designs
+ Sizing ROC studies given a pilot study
+ Simulate ROC studies
+ Can treat binary performance

iMRMC Demo?

https://code.google.com/p/imrmc/



Data Input

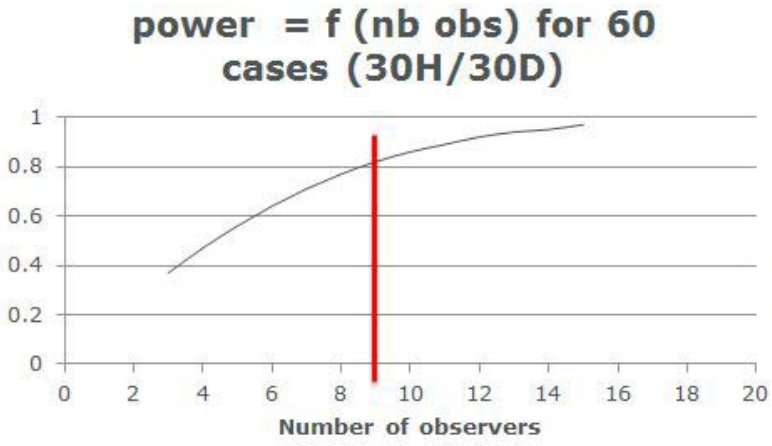
Data Analysis

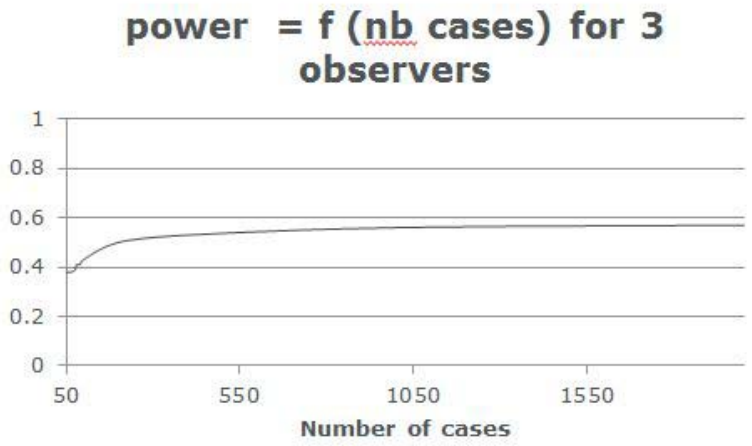
Size a Study

Statistical Analysis and Sizing

- Sizing results example

number of cases	60	60	70	70	80	80	100	100	120	120
number of observers	8	10	8	10	8	10	8	10	8	10
Power	0.77	0.86	0.79	0.88	0.8	0.89	0.84	0.91	0.86	0.93





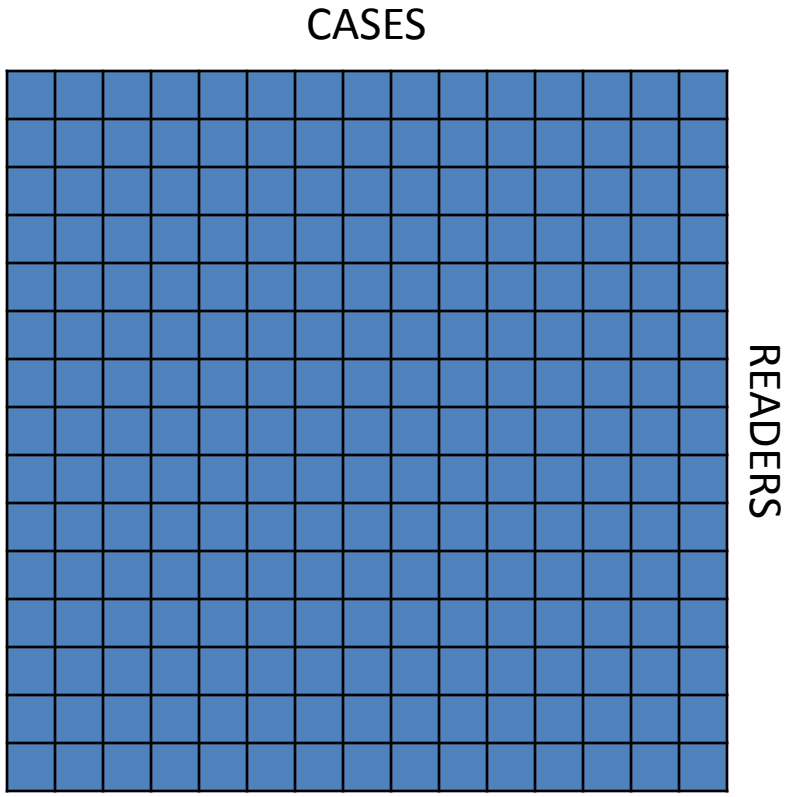
Fully-crossed study design

- Every column indicates a case
- Every row indicates a reader

- Fully-crossed study
  - Every reader reads every case

- Takes a lot of reading time per reader and total

- Lots of redundant information



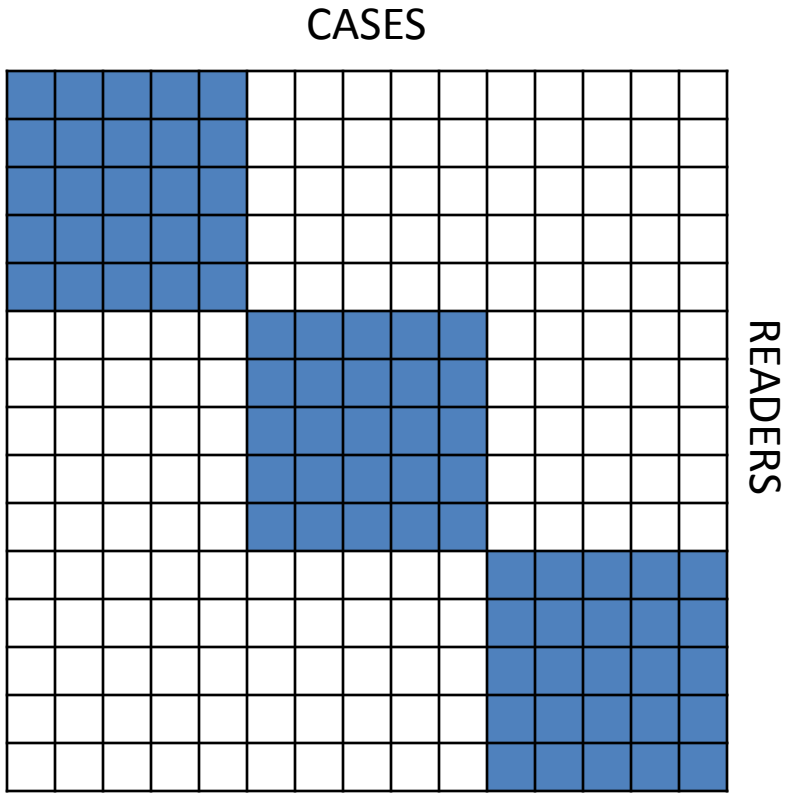
Fully-crossed study design

- Every column indicates a case
- Every row indicates a reader

- Split-plot study
  - Reader only read cases in their group

- BIG REDUCTION IN READING TIME

- MINIMAL IMPACT ON STATISTICAL PRECISION



Obuchowski, N.; Gallas, B. D. & Hillis, S. L. (2012),
'Multi-Reader ROC Studies with Split-Plot Designs: A Comparison of Statistical Methods.'
Acad Radiol, ***19, (12), 1508-1517.***

Split-plot study design

Simulation example where variances are equal

Fully-crossed

- 120 cases
- 6 readers
- 1440 evaluations total
- 240 evaluations/reader

Split-plot (3 groups)

- 120 cases
- 9 readers
- 720 evaluations total
- 80 evaluations/reader

- Fewer readers to recruit

- 50% Fewer evaluations overall
- 33% Fewer evaluations per reader

Closing Remarks

- Reader training can determine study success
  - Resources provided
- MRMC analysis tools are available
  - We want to help: tutorials, features, workflows
- Split-plot study design is revolutionary
  - More bang for the buck
  - VIPER study: 5 study conditions for price of 2
  - Digital Pathology: 3 reading sessions instead of 6

Phases of Evaluation

- Exploratory
  - Early
  - Pilot
- Intermediate
  - Challenge or Stress Test
  - Lab-based
- Advanced
  - Late
  - Clinical use

- Ideal and controlled setting
  - Narrow task
  - Study cases, study readers
- Hypothesis:
  Superiority or Non-Inferiority
  - Compare technologies
- Analysis generalizes to
  - Population of Cases
  - Population of Readers
- Not trying to estimate real-world clinical performance

Phases of Evaluation

- Exploratory
  - Early
  - Pilot
- Intermediate
  - Challenge or Stress Test
  - Lab-based
- Advanced
  - Late
  - Clinical use

- Exploratory
  - Size: Small
  - Scope: Narrow
  - Results: Limited
  - Impact: New Hypothesis
- Advanced
  - Size: Large
  - Scope: Intended Use
  - Results: Definitive
  - Impact: Policy

Phases of Evaluation

- Exploratory
  - Early
  - Pilot
- Intermediate
  - Challenge or Stress Test
  - Lab-based
- Advanced
  - Late
  - Clinical use

Proof of Concept

- Sample size small
- Convenient samples
  vs. Representative
  - Simulations, phantoms, animal models, excised tissue and organs, patients
- PI and collaborator are sole study readers
- Answers
  - What does disease look like?
  - What does normal look like?
  - What can be measured?
  - How might patients benefit?

Phases of Evaluation

- Exploratory
  - Early
  - Pilot
- Intermediate
  - Challenge or Stress Test
  - Lab-based
- Advanced
  - Late
  - Clinical use

Prospective

- Sample size large
- Real world
  - Screening or diagnostic patient population
  - Patient care clinicians
  - Clinical reports, outcomes
  - Absolute performance
  - Meta and cost-benefit analyses
- Supports
  - Current practice guidelines
  - Policy and payment

Intermediate Phase
Challenge Test, Stress Test

- *Compare* new modality to current practice
  - Better (Superiority hypothesis)
  - Equivalent (Non-Inferiority hypothesis)

- Ideal, tightly-controlled, lab-based study
  - Readers blind to patient info
  - Task is narrow, quantitative
  - Calibrated equipment and tight protocols

Intermediate Phase
Challenge Test, Stress Test

- Challenging cases with and without disease
  - May not mimic intended use population
  - Creative sourcing to build study population
  - Enrich representation of key subgroups
    - Known or suspected differences
    - Statistical sub group analysis warranted?
  - Eliminate cases that don't help comparison
    - Obvious disease, obvious normal

- Technology Evaluation Not Clinical Performance

Aims of a Reader Study: Intermediate Phase

- Task: Doctor Evaluates Patient Image
  - Narrow, Singular, Clear vs. Clinically Relevant
  - Data: Categorical, Ordinal, Interval, Ratio

- Data and Reference Standard Dictate Endpoint
  - Binary reference → Se/Sp, Area under ROC
  - Multi-level reference → Concordance

Aims of a Reader Study: Intermediate Phase

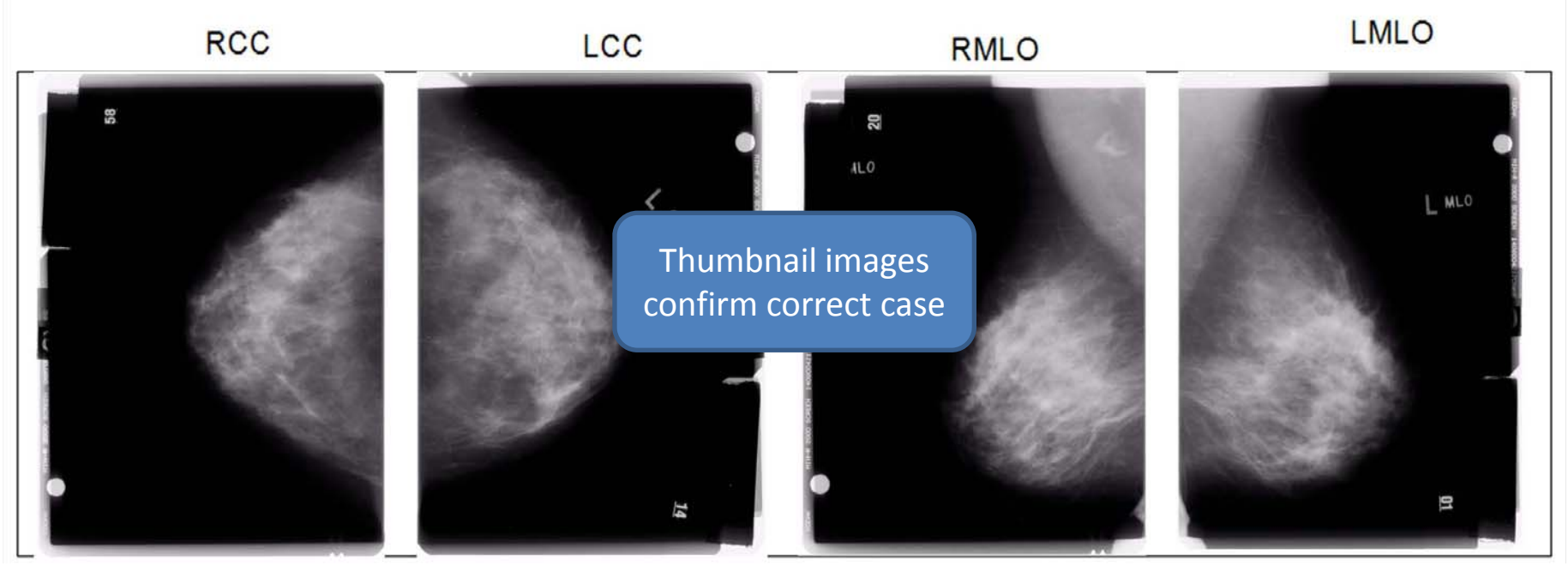
Hypothesis testing: Assume what you want to disprove

- Better = Superiority
  - H0: Endpoint New Modality – Endpoint Current Practice = 0
  - H1: Endpoint New Modality – Endpoint Current Practice > 0
- Equivalent = Non-Inferiority
  - H0: Endpoint New Modality – Endpoint Current Practice = Non-Inferiority Margin
  - H1: Endpoint New Modality – Endpoint Current Practice > Non-Inferiority Margin

Sample eCRF: QC check

Link key info to each observation

Reader ID	Modality	Case ID	View Box #



Sample eCRF: ROC in 2 steps

Would you recall patient?

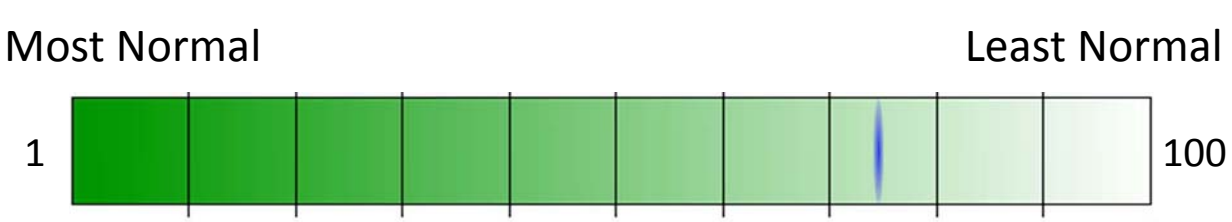
- ○ Yes
- ● No

Simple question with clinical relevance
== Operating point on ROC curve

Being more quantitative in reporting your *Numeric Rating*:

- Are there no dense areas and no abnormal findings?
  - If so, perhaps your *Numeric Rating* should be 1-25?
- Are there dense areas or benign findings, but not enough to prompt a decision to recall?
  - If so, perhaps your *Numeric Rating* should be 75-100.
- Are the visual cues somewhere in the middle?

Reiterate Instructions



Numeric Score

	7	5

Allow Quantitation
Allow Control

Sample eCRF: ROC in 2 steps

Would you recall patient?

- (●) Yes
- (○) No

Different "clinical" decision
== Threshold @ 100

Being more quantitative in reporting your Numeric Rating:

- Are there only a few inconclusive visual cues prompting your decision to recall?
  - If so, perhaps your Numeric Rating should be 101-125?
- Are there many definitive visual cues prompting your decision to recall?
  - If so, perhaps your Numeric Rating should be 175-200.

Are the visual cues somewhere in the middle?