Pilot Reader Studies Comparing Whole Slide Images with Different Gamma Settings

Division of Imaging and Applied Mathematics, OSEL/CDRH/FDA:

Brandon D. Gallas, PhD

Marios A. Gavrielides, PhD

Adam Wunderlich, PhD

Molecular Pathology and Cytology Branch, DMGP/OIR/CDRH/FDA

Jeffrey D. Seidman, MD

Laboratory of Pathology, Center for Cancer Research, NCI/NIH:

Stephen Hewitt, MD/PhD

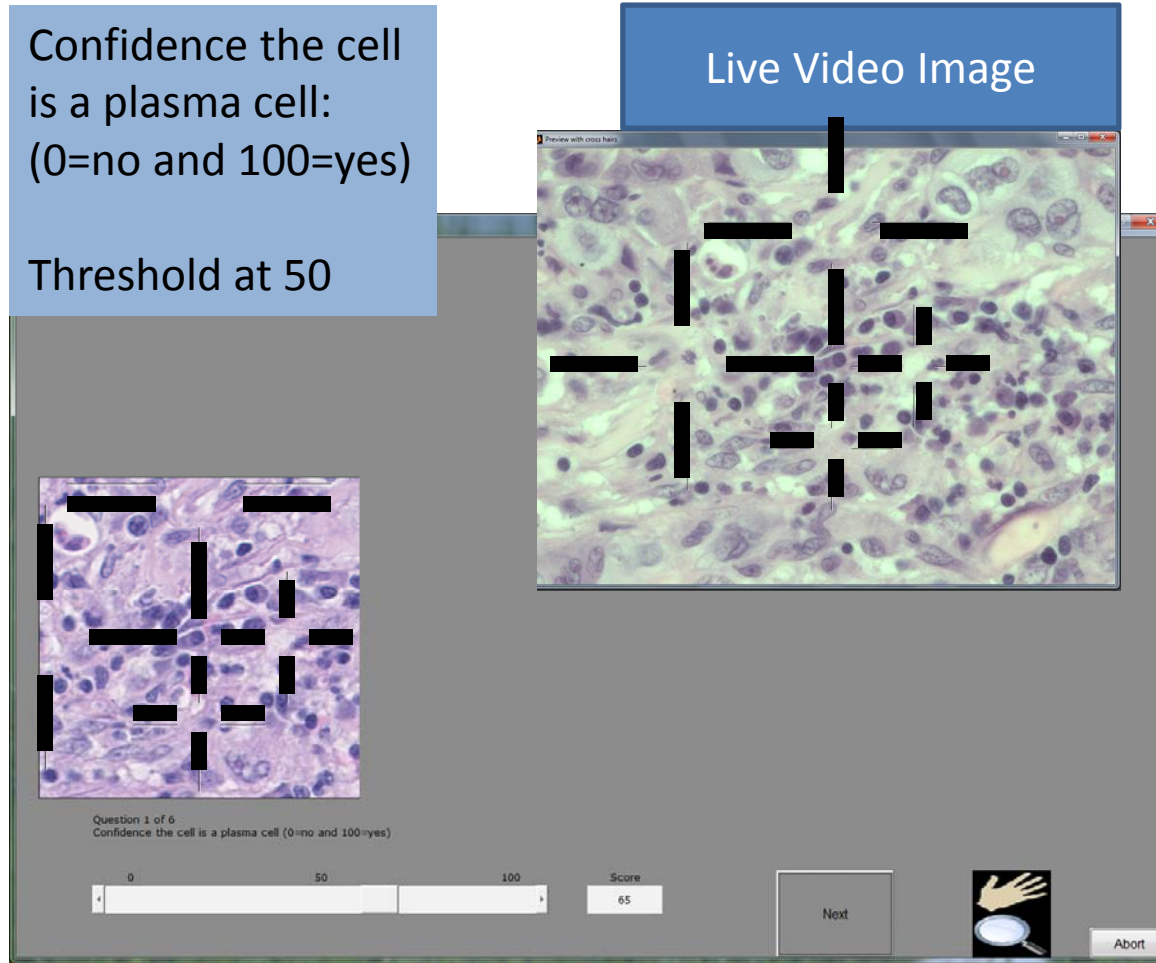Jason Hipp, MD/PhD

Outline

- Subject: <u>Task-Based</u> Evaluation of Whole Slide Imaging

- This Talk: Feasibility Studies
  - Develop data collection methods
  - Develop data analysis methods
  - Execute reader studies

- Current Goals: Get experience and identify problems
  - Study design and analysis
  - Imaging and reading protocol and training
  - Software bugs

Data Collection Methods

- **eeDAP**
  - *evaluation environment for Digital and Analog Pathology*
  - Software and Hardware

  - **KEY**: Registration between
  digital whole slide image and microscope slide

  - **Registration Reduces or Eliminates Variability**
  Search Training, Search Ability, Evaluation Area

  - **Software:** http://code.google.com/p/eedap/

eeDAP Data Collection GUI

Confidence the cell
is a plasma cell:
(0=no and 100=yes)

Threshold at 50

Live Video Image

- *Digital Mode*

- *MicroRT Mode*

  Pathologist
  – Engaged with
    microscope

  Administrator
  – Operates GUI
  – Enters Data
  – Checks and
    Maintains Good
    Registration

Question 1 of 6
Confidence the cell is a plasma cell (0=no and 100=yes)

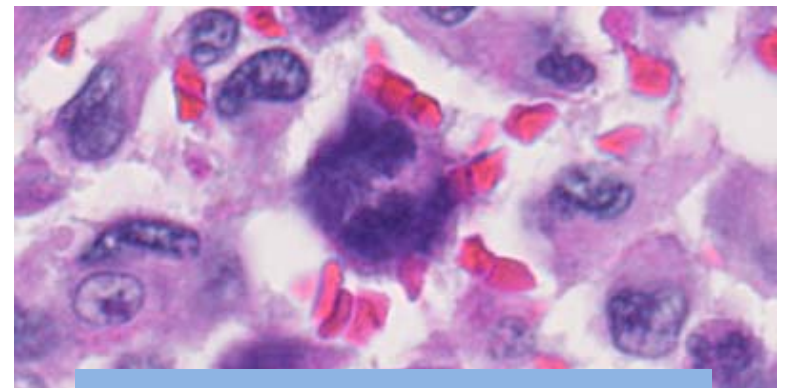0   50   100   Score

65

Next   Abort

Color Differences Observed

- eeDAP viewer
  - Darker
  - Less contrast in nucleus

- Native viewer
  (developed by scanner mfr)
  - Brighter
  - More contrast in nucleus

Sarcoma: Candidate Mitotic Figure
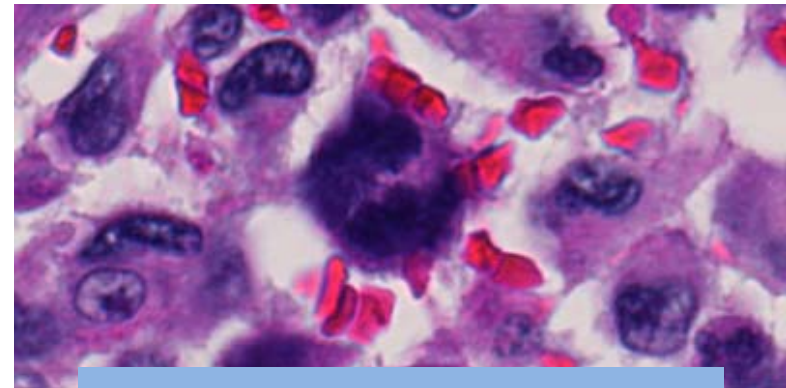
eeDAP viewer == Gamma = 1.0

native viewer == Gamma = 1.8

Hypothesis

- Can a pathologist identify mitotic figures as well?
  - Image viewer gamma = 1.0 — New Modality
  - Vs.
  - Image viewer gamma = 1.8 — Comparison Modality

- Non-Inferiority Hypothesis

H0: | Agreement (Gamma=1.0) | − | Agreement (Gamma=1.8) | = | Allowable Margin Of Inferiority |
New / Default

H1: | Agreement (Gamma=1.0) | − | Agreement (Gamma=1.8) | > | Allowable Margin Of Inferiority |

Pathologist With Microscope Is Reference For Agreement

Uncertainty in Reader Studies
Not Trivial

- Variance of Agreement

$$\boxed{\text{Variance from Readers}} + \boxed{\text{Variance from Cases}} + \boxed{\text{Error}}$$

| Reader Skill | Case Difficulty | Reader Jitter |

- Binary Data: Rate of Agreement
  - Weijie Chen et al. Talk Yesterday
  - SPIE Journal of Medical Imaging (Submitted)
  - Software:
    http://code.google.com/p/imrmc/wiki/iMRMC_Binary

Agreement (101-point Data): Concordance

- ## Why not just binary agreement?
  - – More information
  - – More statistical power
  - – Smaller studies

Agreement (101-point Data):
Concordance

Experiment

- Draw two cases from population.

- Compare scores from
  - Pathologist/WSI
  - Pathologist/Microscope.
    (reference)

Results

1. **Concordance**

Cases ranked in same order

2. **Discordance**

Cases ranked in opposite order

3. **Tie** by first pathologist

4. **Tie** by second pathologist

5. **Tie** by both pathologists

Feasibility Studies

- Task: Differentiate Cells as Mitotic Figures or Not
  - Score: 101 point confidence scale
  - Score: Threshold at 50 -> Positive/Negative

- Cases
  - 25 expert identified target cells
  - 25 random candidate cells

- Readers
  - Study: 1 pathologist, 3 collaborators, 1 novice
  - Reference: 1 pathologist

Agreement (101-point Data): Mitotic Figures
Pathologist Study Reader vs. Pathologist on Microscope

Scatter plot of 50 observations
Size of circle is proportional to frequency of observation
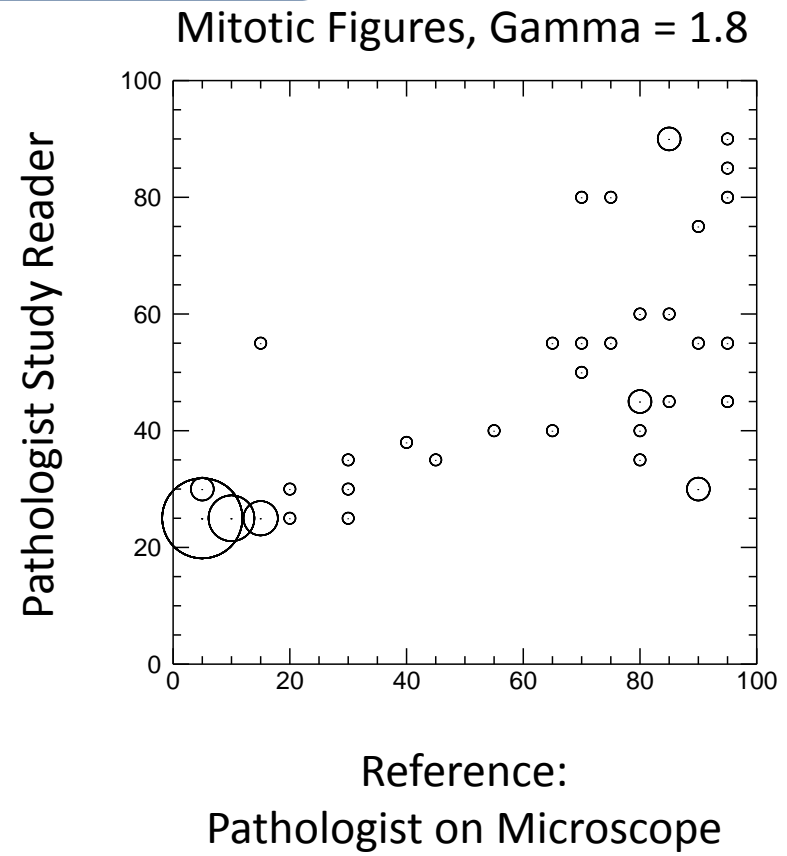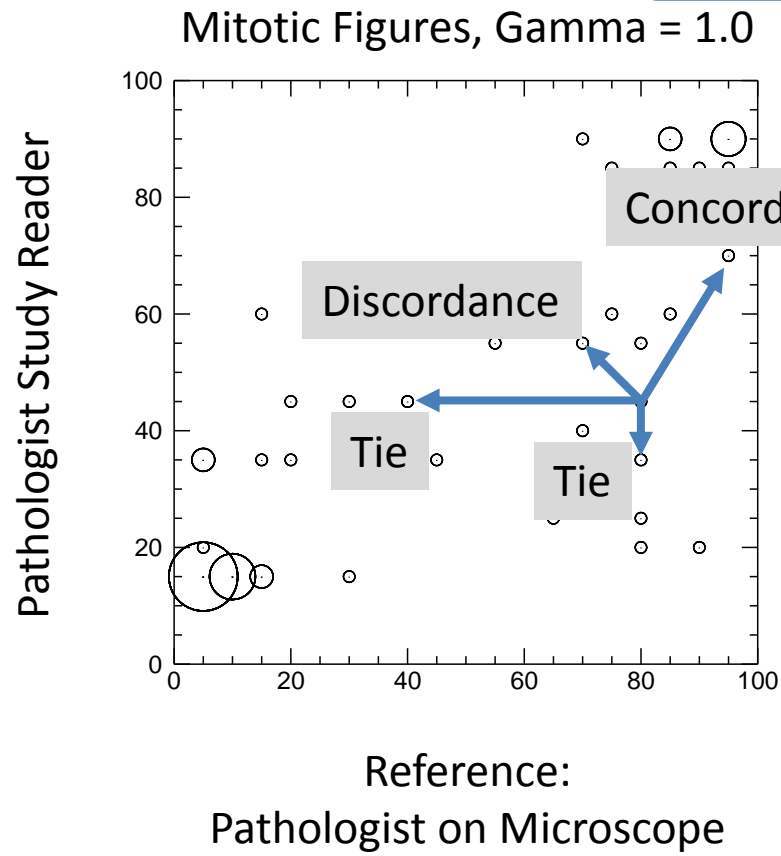
Mitotic Figures, Gamma = 1.0

Mitotic Figures, Gamma = 1.8

Pathologist Study Reader

Reference:
Pathologist on Microscope

Agreement (101-point Data): Mitotic Figures
Pathologist Study Reader vs. Pathologist on Microscope

Concordance: 856/1225 = 0.70

No Ties: 1024/1225 = 0.84
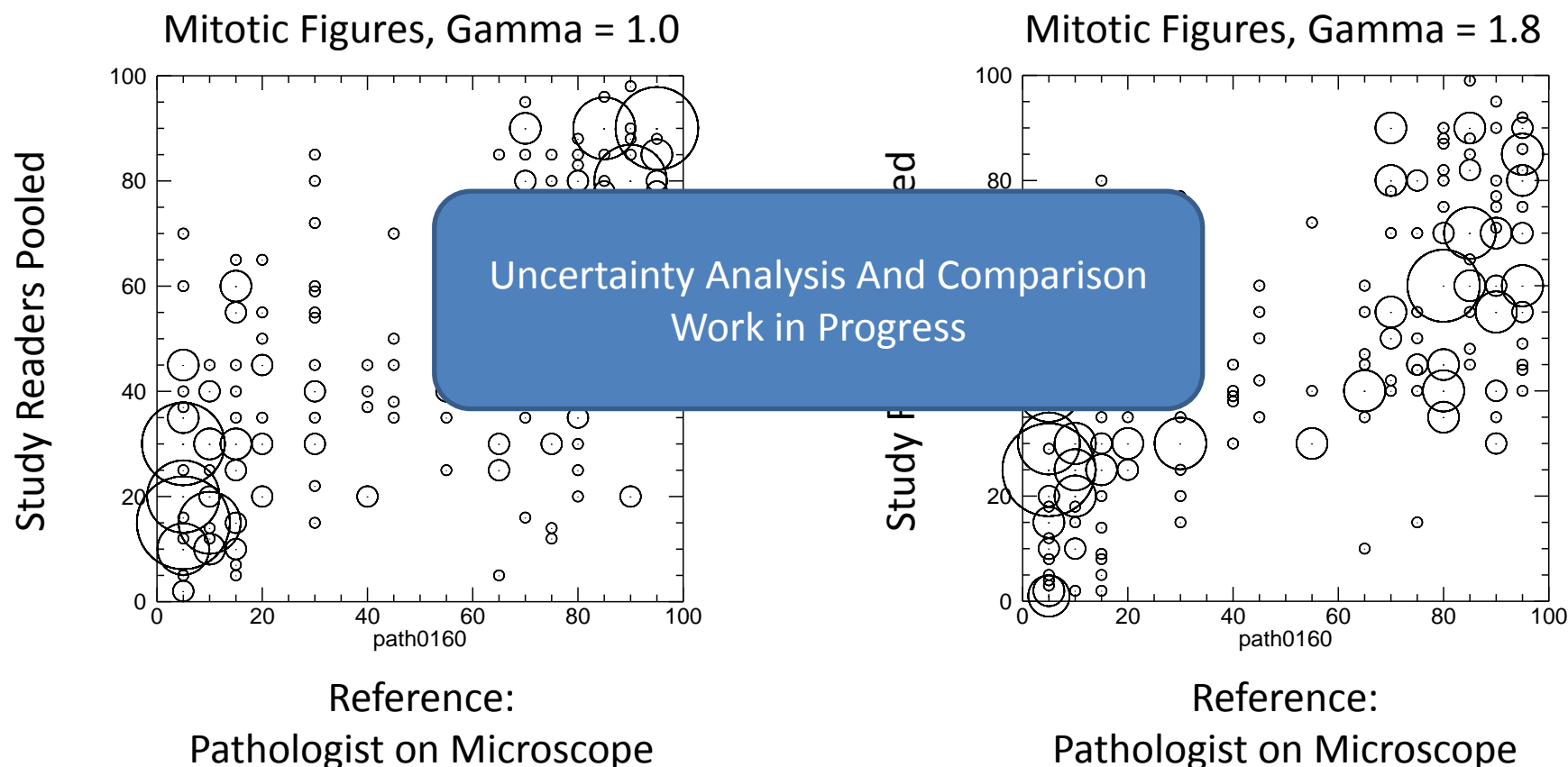
Concordance: 850/1225 = 0.69

No Ties: 1001/1225 = 0.82
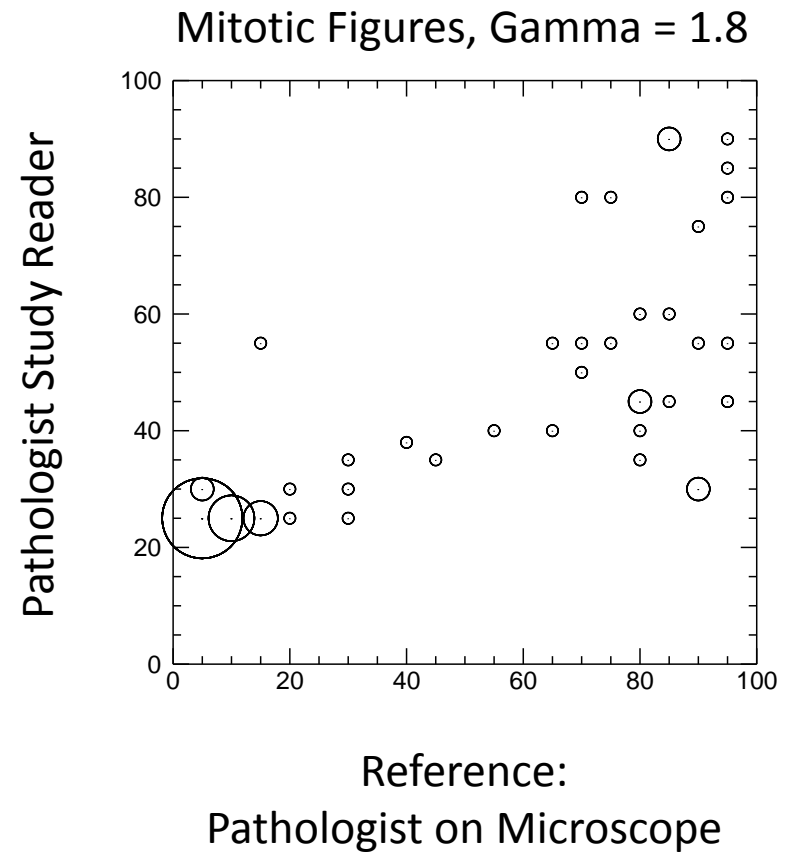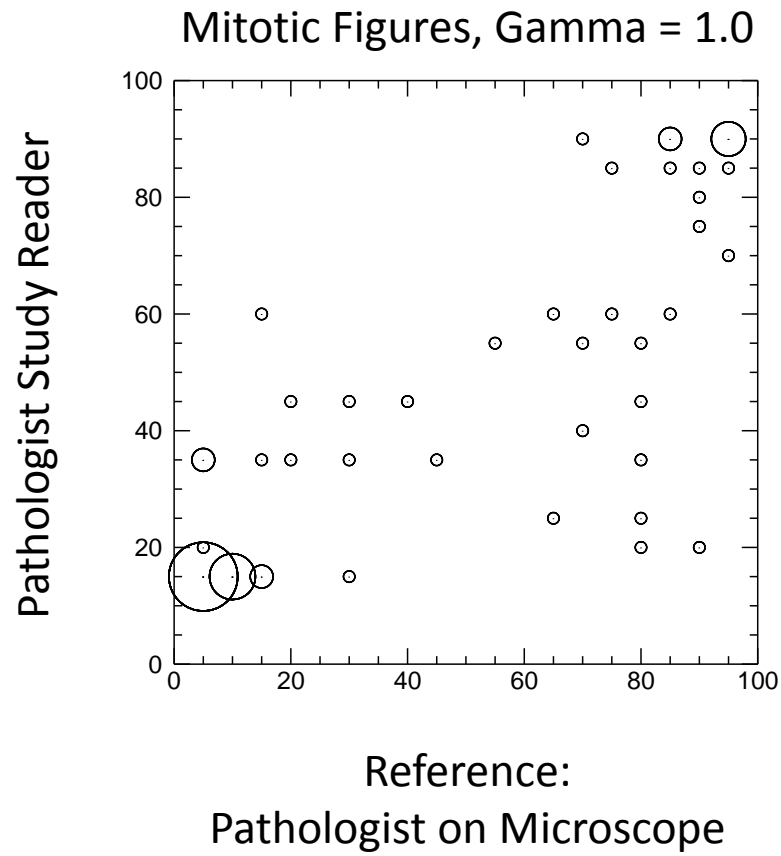
Agreement (101-point Data): Mitotic Figures
Average over Study Readers

Concordance: 862.2/1225 = 0.70
No Ties: 1058.8/1225 = 0.86

Concordance: 861.2/1225 = 0.70
Any Tie: 1058/1225 = 0.86

Mitotic Figures, Gamma = 1.0

Mitotic Figures, Gamma = 1.8

Uncertainty Analysis And Comparison
Work in Progress

Reference:
Pathologist on Microscope

Reference:
Pathologist on Microscope

Summary of Results

- Feasibility Studies: Mitotic Figures

- Agreement with Pathologist using Microscope
  - Image viewer gamma = 1.0

    NOT WORSE
  - Image viewer gamma = 1.8

- Variance analysis is a work in progress

- Limitations:
  - Biased Case Selection
  - Uncalibrated Monitors

Future Work

- Future work:
  - Uncertainty analysis for 101-point data
    (is there more power?)

  - Push gamma, cause loss in performance

  - Investigate other tasks

  - Link image quality to task performance
    (color, dynamic range, contrast, focus/resolution)

  - Compare WSI to Microscope

More Details

- More details on "eeDAP"
  - Software/Hardware Info
  - Registration Algorithms
  - Imaging specifications
  - Color: software dependent tone reproduction curves

- SPIE Medical Imaging proceedings paper

- http://code.google.com
  - project "eeDAP"
  - Matlab source code
  - Precompiled, stand-alone, license free application

- Non-inferiority analysis Binary Data
  - Weijie Chen et al.

  - Talk Yesterday

  - SPIE Journal of Medical Imaging (Submitted)

  - http://code.google.com
    - Project: iMRMC
    - Package: iMRMC_Binary

Working Group Invitation:

- Image Quality in Whole Slide Imaging And Pathologist Performance

- Stakeholders: Industry, Hospitals, Academia, and Government

- Develop and standardize WSI image quality evaluations.
- Design and execute experiments: pathologist performance
- Create and disseminate methods, tools, examples, and recommendations

- Contact Brandon.Gallas@fda.hhs.gov