# Practical Systems in Biomedicine

## A Personal Perspective

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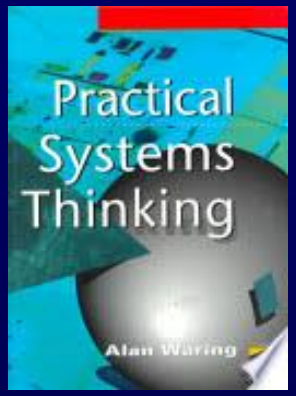
# Approach

- How can we think about systems?
- How can we think about "practical systems"?
- Observations about "my" biomedical systems
  - What they did
  - Who used them and why
  - Their practical value (or lack thereof)
- Error and failure modes – do we neglect them?
- Other successful biomedical system examples and future opportunities
- Closing thought

# How Can We Think About Systems?

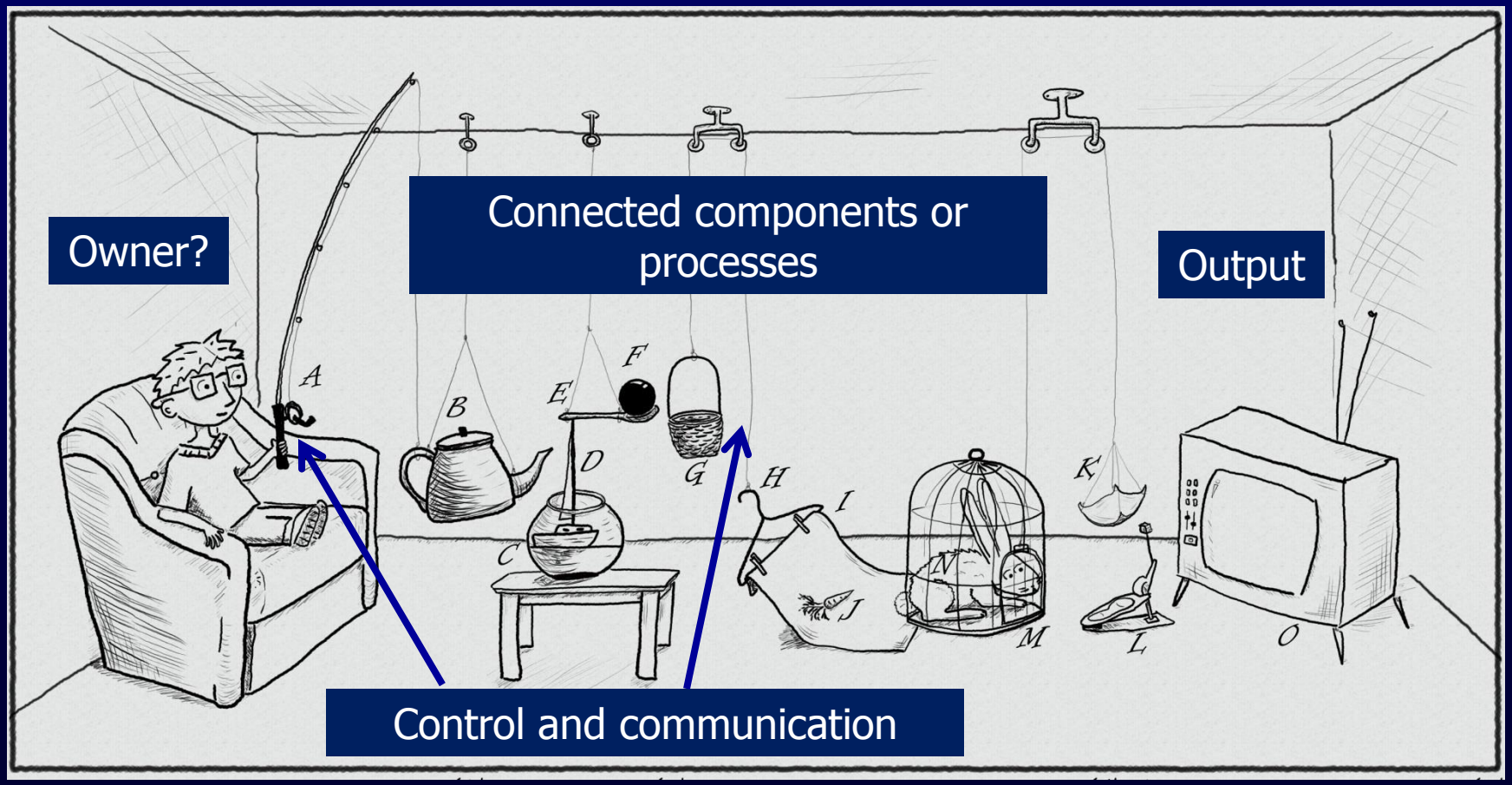



There is no common agreement on the definition of a "system", but…

- A system does something (there are processes and outputs).
- Addition or removal of a component changes the system.
- A component is affected by its inclusion in the system.
- Components are perceived to be related in hierarchical structures.
- There are means for control and communication which promote system survival.
- The system has emergent properties, some of which are difficult to predict.
- The system has a boundary.
- Outside the boundary is a system environment that affects the system.
- The system is owned by someone.

-Alan Waring

# System? Practical?



- Reuben Lucius Goldberg (1883-1970) popularized these systems
- They came to be called “Rube Goldberg machines”

They symbolize, he said,…

**“Man’s capacity for exerting maximum effort to achieve minimum results”**

# Basic Law of Practical Systems?

- Whatever we call a "practical system"…
- …we want useful results*
- …for reasonable expenditure* of effort
  - (or money, risk, time)

*As measured by real system users

# Three Factors Affecting How We Think About Practical Systems

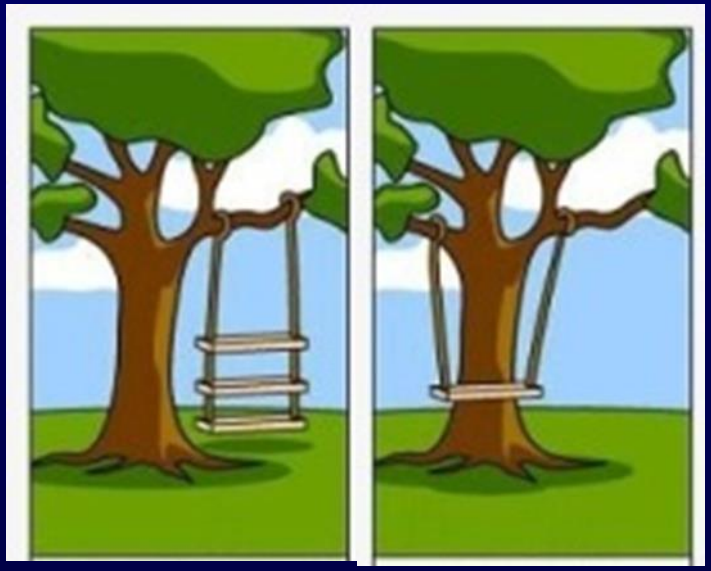
- Practicality of development
- Practicality of operation
- Scale of system

# Practicality of Development…

# Practicality of Development…

How the customer explained it

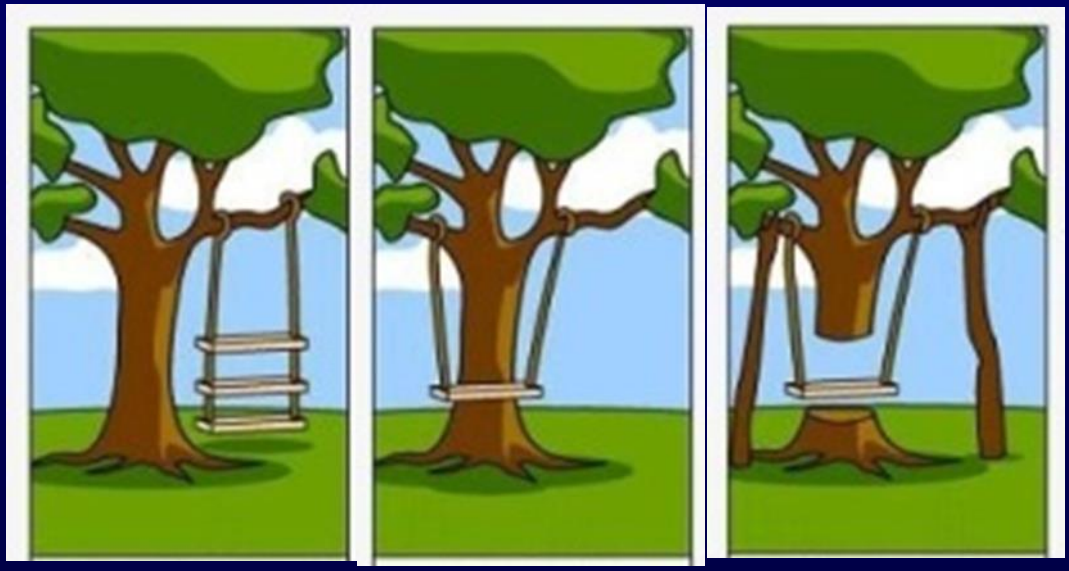
# Practicality of Development…



How the customer explained it

How the project leader understood it

# Practicality of Development…

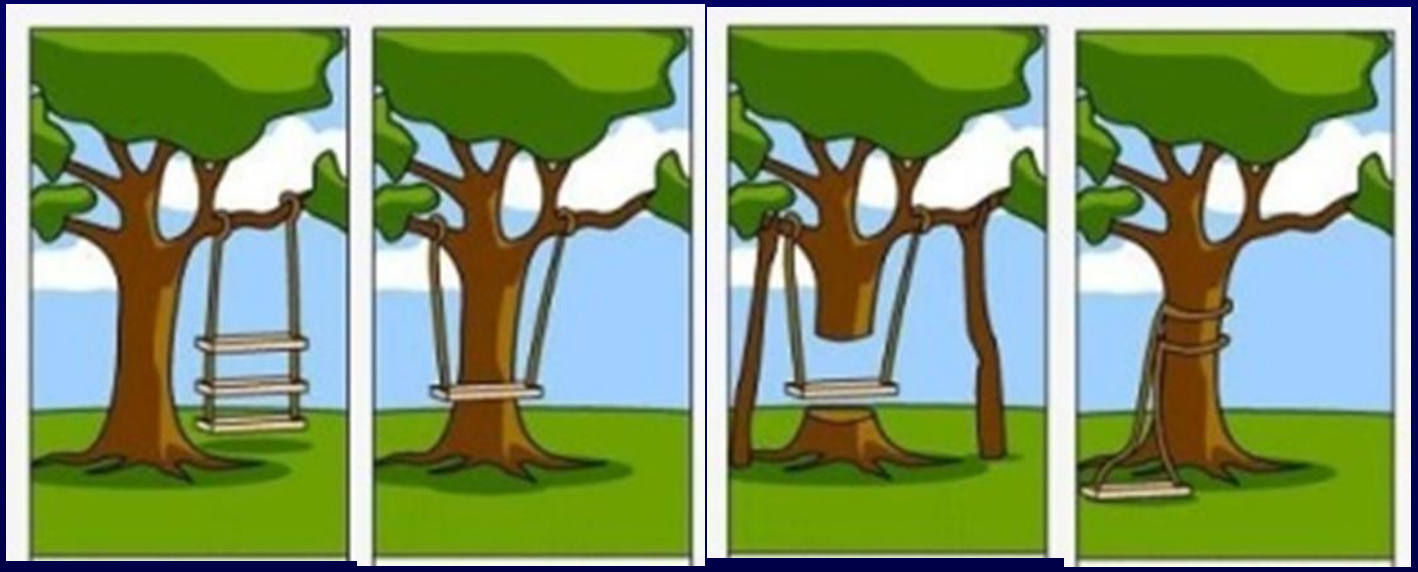


How the customer explained it

How the project leader understood it

How the systems analyst designed it

# Practicality of Development…



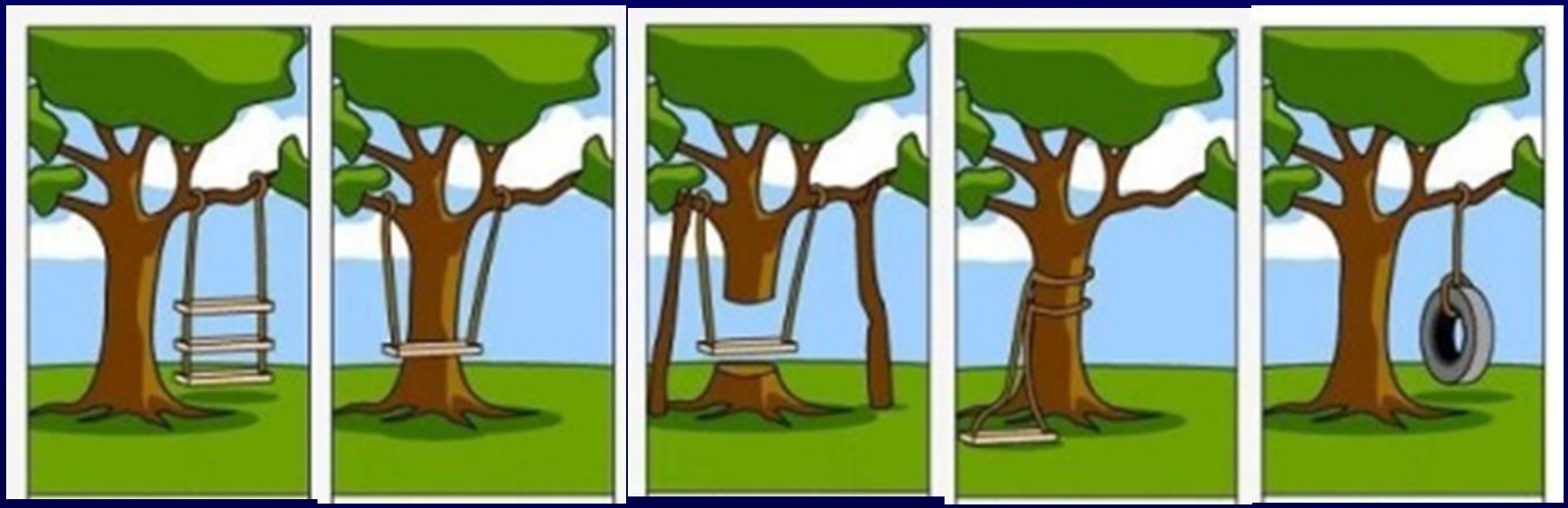
How the customer explained it

How the project leader understood it

How the systems analyst designed it

How the programmer coded it

# Practicality of Development…



How the customer explained it

How the project leader understood it

How the systems analyst designed it

How the programmer coded it

What the customer really needed

# …or Practicality of Operation

# …or Practicality of Operation

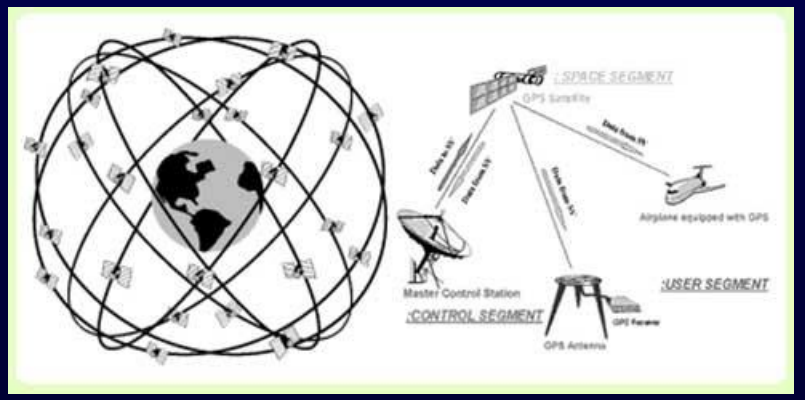
# Practicality and Scale

**Very large systems come with "order(s) of magnitude factors"**

**Space Shuttle**

Or

- **Complexity**
- **Funding**
- **Staffing**
- **Perhaps geopolitical/national priority factors**



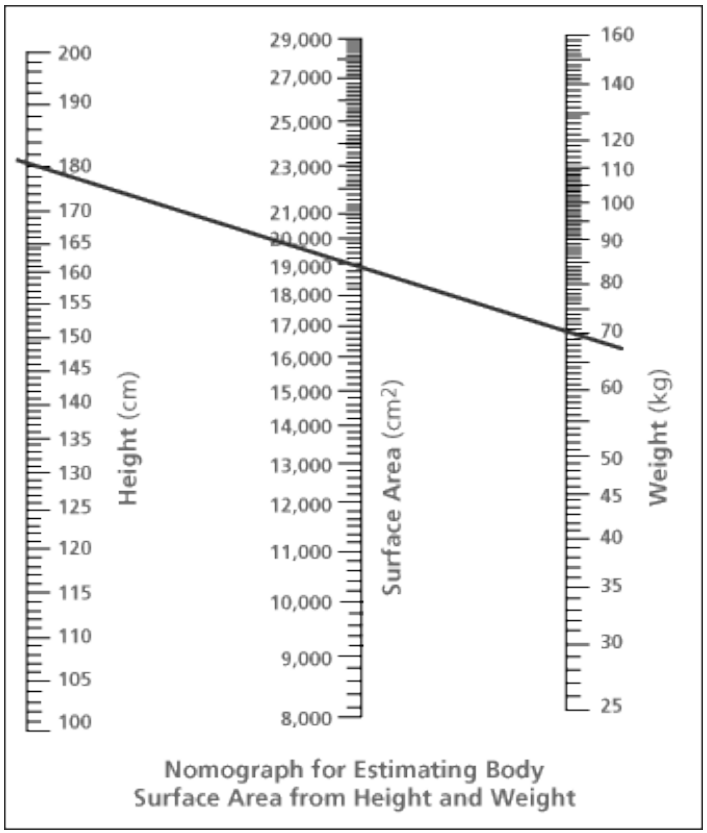

**Global Positioning System**

# This Talk Focuses On Biomedical Systems Where…

- Practicality means reasonable payoff for reasonable effort
- We look mainly at practicality of operation
- The scale is small…
  - Developed/operated by individuals or small teams
  - Type of effort carried out by academic labs, small business, small gov. labs

- **Complex algorithms are not always essential to have significant impact.**
- User value goes up as dependency on computer specialists goes down.
- Engineers need the basic vocabulary and concepts of their medical application domain; medical experts need to be able to interpret quantitative system output.
- Small systems have a natural fit for problem- solving in low-resource areas.
- Advanced algorithms may provide critical assistance to the clinician, but workflow can be a showstopper.
- Attention to error and failure modes may yield the biggest payoff in building practical systems.

# A Very Early Small "System"



Nomograph for Estimating Body Surface Area from Height and Weight

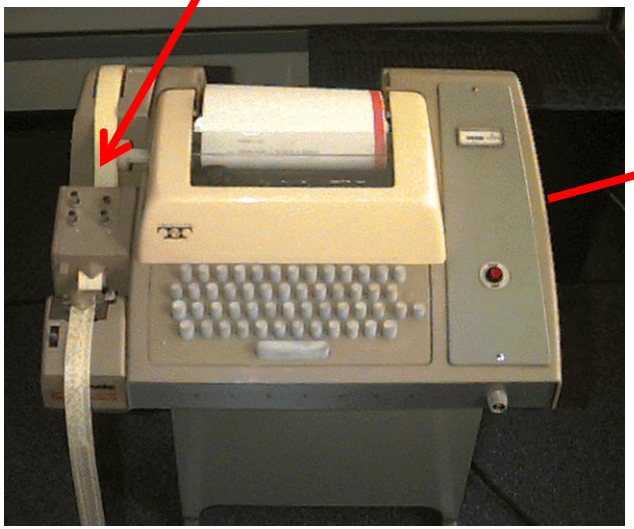
- **Walter Reed Hospital Cardiology Dept., Washington, DC (1972)**
- **Cardiac output measured in liters/min/body surface area**
- **Body surface area calculated with <u>nomograph</u>**

# Computer-Based Medical System (CBMS)

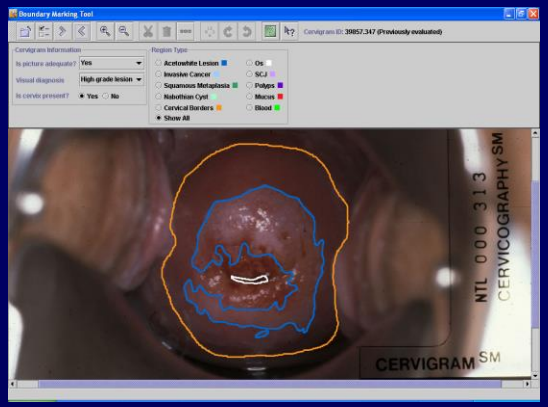
$$BSA\ (m^2) = \sqrt{\frac{Ht\ (cm) \times Wt\ (kg)}{3600}}$$

**BSA Formula**

**Paper Tape**



**Minicomputer**



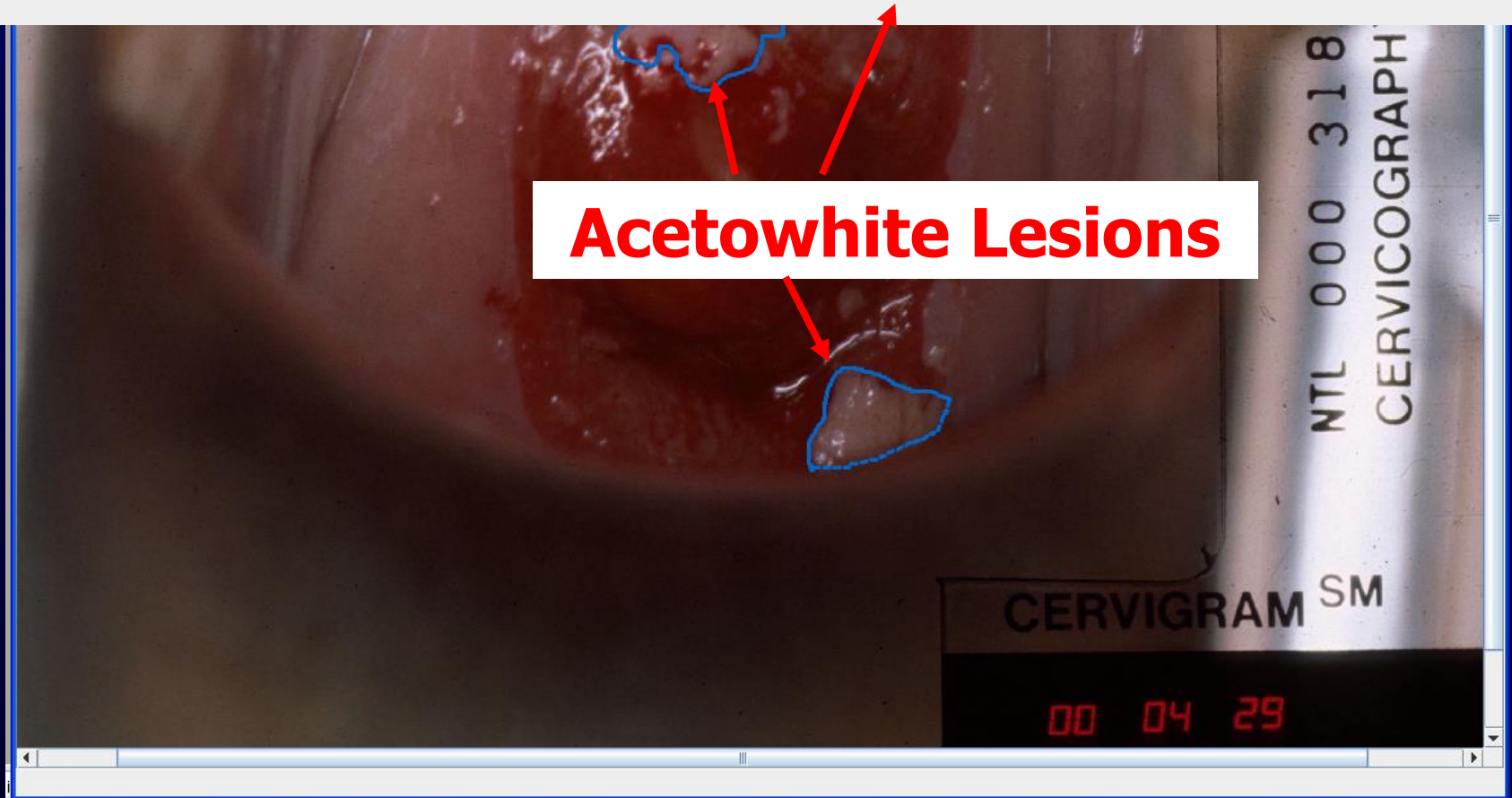

# Boundary Marking Tool
## (NLM/NIH ~2006)

- Graphical annotation (manual segmentation)
- Recording of diagnostic data
  - By region
  - For image as a whole
- Web-based
  - Facilitates multi-observer studies
- We distribute under open-source license

**Primary developer: Leif Neve**

Region Type

- (●) Acetowhite Lesion ■
- ( ) Cervical Borders ■
- ( ) Show All
- ( ) Hide All



# Boundary Information

Acetowhite Lesion Information

Punctation 2

Color

Mosaic

Marg

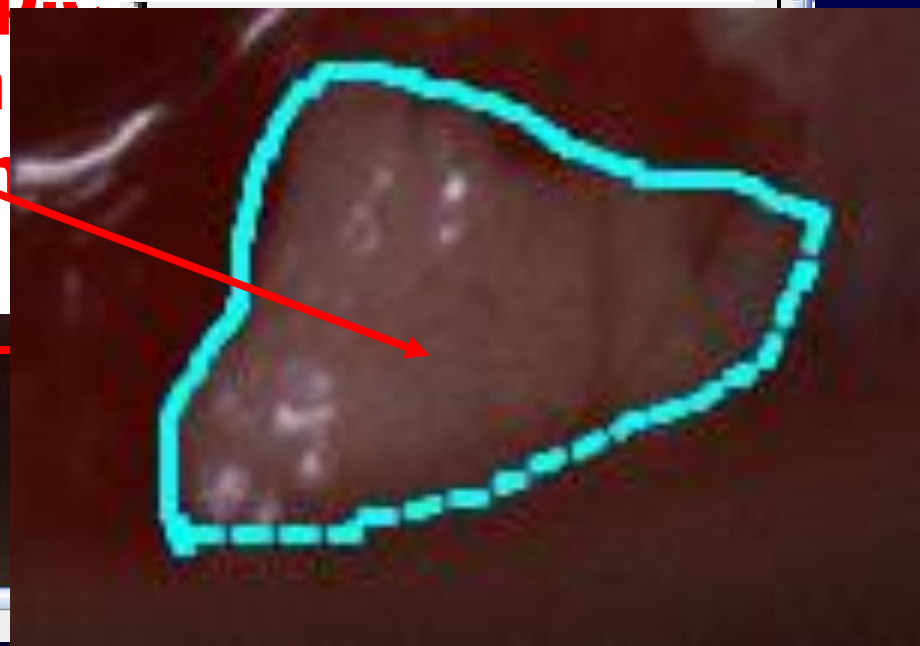
Visual diag

HSIL

- 0 Fine Punctation
- 1 None
- 2 Coarse Punctation

…using … and terminol… cop… practic… ua… features such as lesion color…

…or visual patterns on the lesions caused by vessels near the surface…




Cervigram Information
Picture adequate? Yes
Visual diagnosis High-grade lesion
42030.429 (Previously evaluated)
Observer 1
Visual diagnosis…
… and lesion marking…
… are subject to (sometimes large) inter-observer variability
NTL 000 318
CERVICOGRAPHY SM
CERVIGRAM SM
00 04 29


Cervigram Information
Picture adequate?
No--Poor cervical position
Visual diagnosis
Invasive cancer
030.429 (Previously evaluated)
Observer 2
Visual diagnosis…
… lesion marking…
NTL 000 318
CERVICOGRAPHY SM
CERVIGRAM SM
00 04 29

| |
|---|
| Age-Related Changes of the Cervix Influence Human Papillomavirus Type Distribution. *Cancer Research. January 2006;66(2):1218-24.* |
| Colposcopy at a Crossroads. *American Journal of Obstetrics and Gynecology. August 2006; 195(2):349-53.* |
| Interobserver agreement in the evaluation of digitized cervical images. *Obstetrics and Gynecology. 2007;110:833-40.* |
| Visual Appearance of the Uterine Cervix: Correlation With Human Papillomavirus Detection and Type. *American Journal of Obstetrics and Gynecology. July 2007;197(1):47.e1-47.e8.* |
| Interobserver Agreement in the Assessment of Components of Colposcopic Grading. *Obstetrics & Gynecology. June 2008;111(6):1279-1284.* |
| The Accuracy of Colposcopic Grading for Detection of High-Grade Cervical Intraepithelial Neoplasia. *Journal of Lower Genital Tract Disease*. 2009;13(3):137-144. |

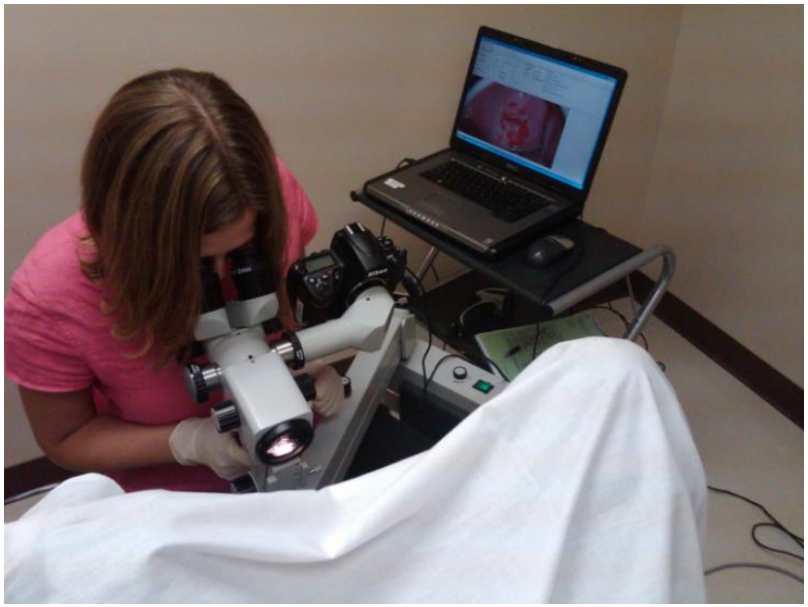
# Practical Value of the BMT: National Cancer Institute (NCI) Biopsy Study

- Each year in the U.S.
  - 3 million women with abnormal results on cervix screening undergo colposcopic exams
  - Usually, one biopsy is taken, at the visually-worst site

- PROBLEM: NCI analyses have shown that 30-50% of high-grade lesions are being missed.

- QUESTION: Will new protocol, taking more than one biopsy, alleviate this situation?

# Study to discriminate precancer from HPV infection (BIOPSY Study)



- What is the incremental benefit of taking multiple biopsies?
- Can we better standardize colposcopy-biopsy?
- How are multiple lesions on the cervix related?
- Which types cause individual lesions?

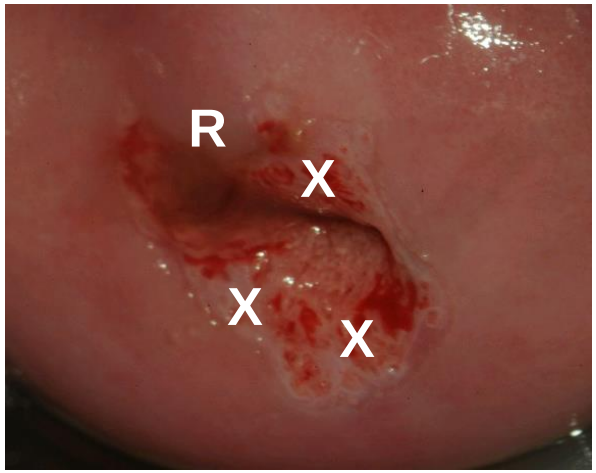
**Setting:** University Oklahoma colposcopy clinic

**Recruitment goal:** 800-1000 women from a referral population without prior treatment

**Approach:** Systematic, extended biopsy protocol with digital documentation

Slide used by permission of Dr. Nicholas Wentzensen, NCI/NIH/USA

# Modified biopsy protocol




| | CIN3+ | <CIN3 |
|---|---|---|
| **Risk factor/ biomarker +** | **A+a** | **B-a** |
| **Risk factor/ biomarker -** | **C+c** | **D-c** |

Odds ratio: (A+a)(D-c)/(B-a)(C+c)

Colposcopy-biopsy

Reduce misclassification

- Up to four biopsies are taken, if less than 4 targeted biopsies, one random is added
- Biopsy impression is recorded, biopsies are ranked and evaluated individually

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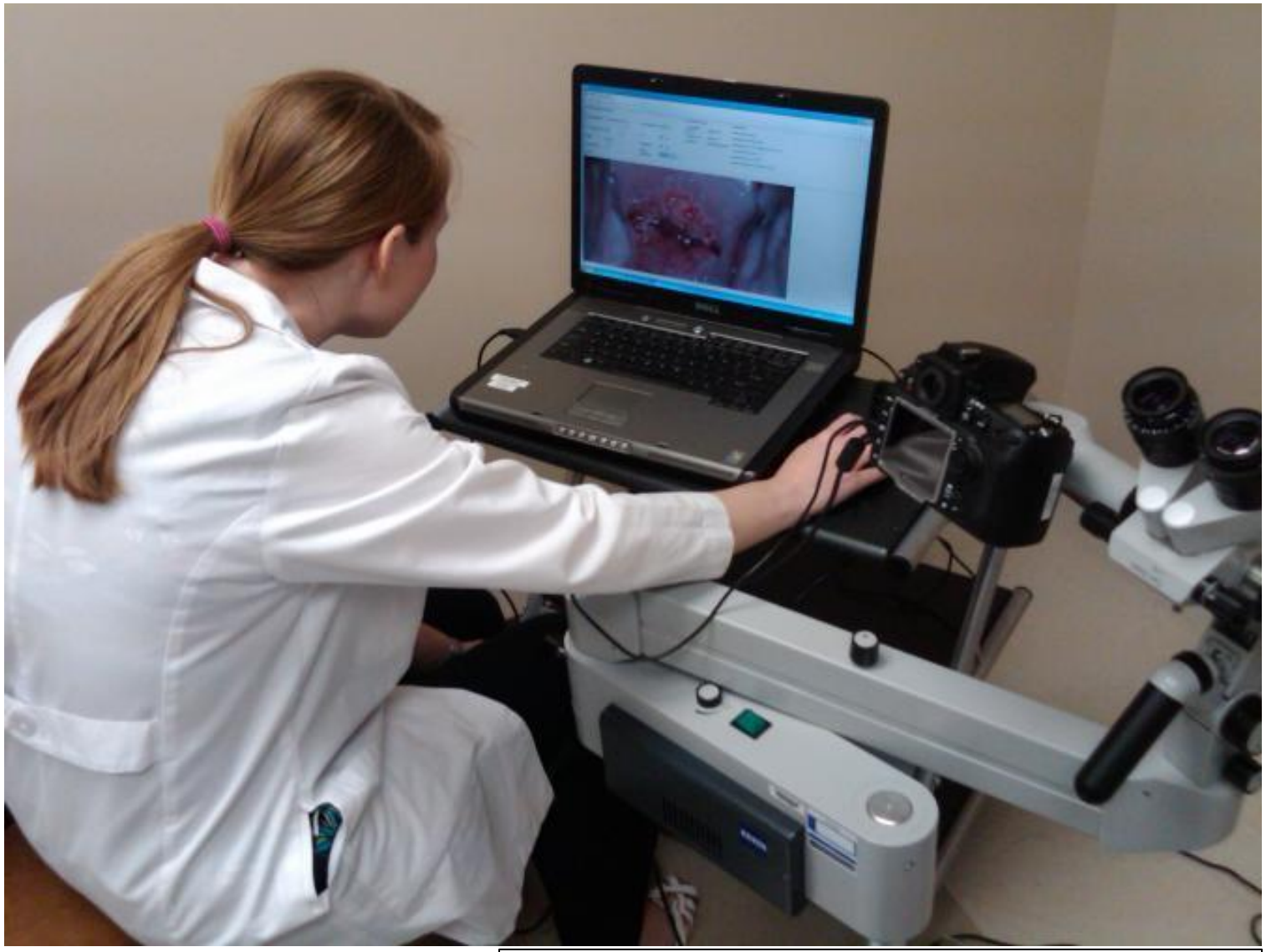
# Image annotation



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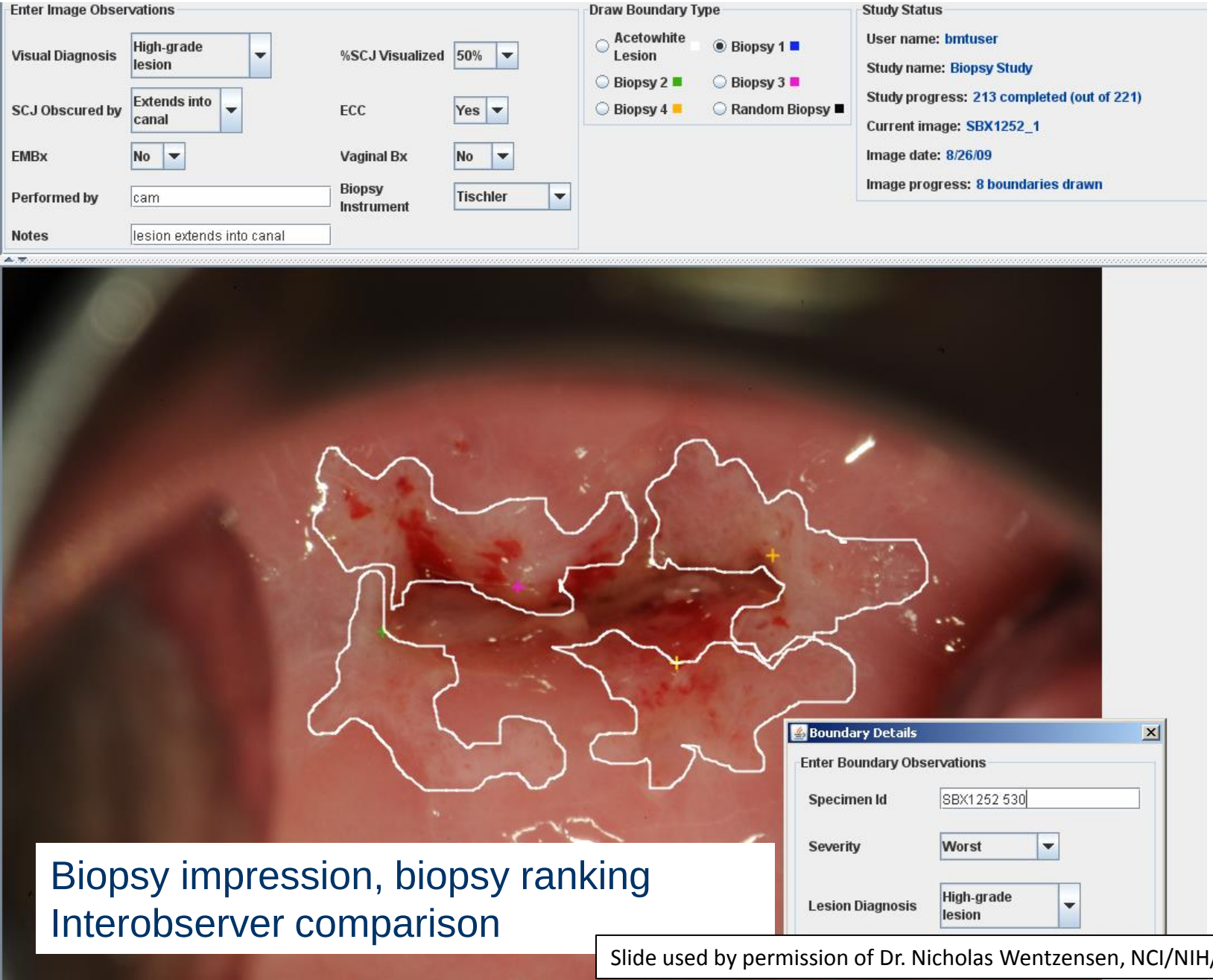
# Data analysis- biopsies




Biopsy impression, biopsy ranking
Interobserver comparison

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Multiple Biopsies and Detection of Cervical Cancer Precursors at Colposcopy

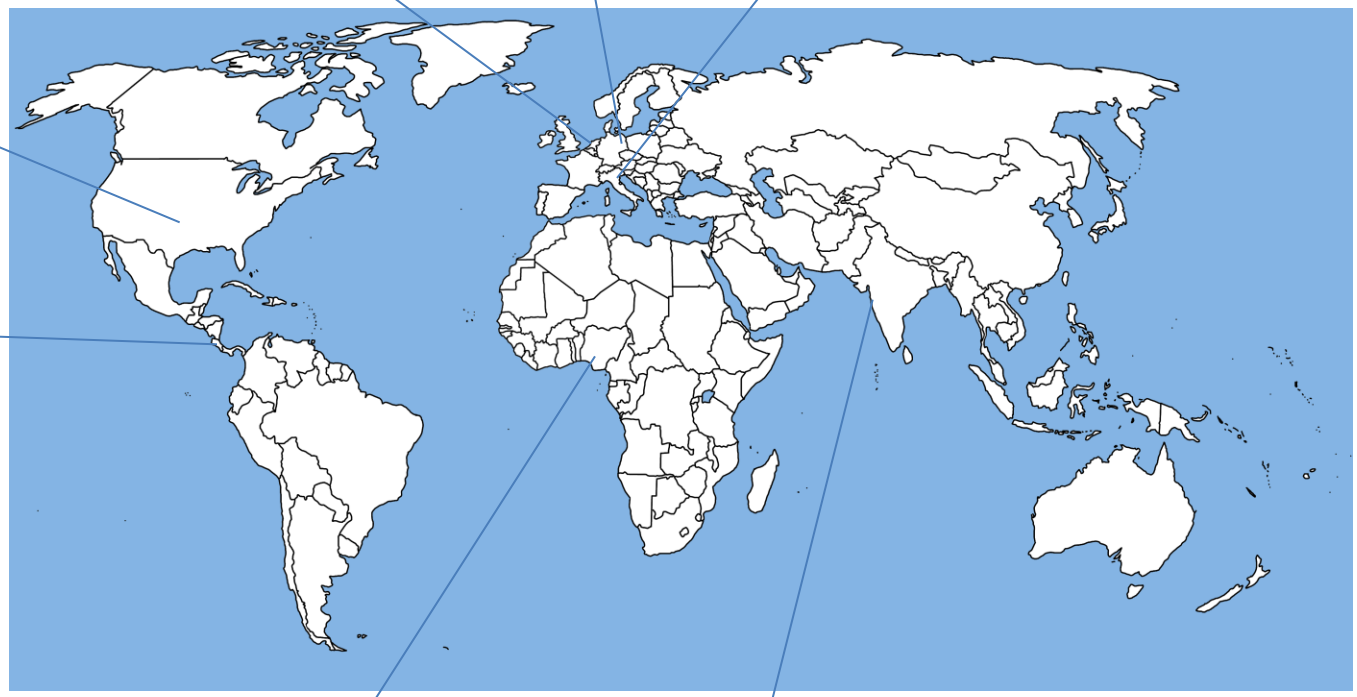
The biopsy results determine whether excision of the lesion is required. Colposcopy with a single biopsy can fail to detect HSIL. This study involved 690 women who had up to four distinct lesions biopsied. The sensitivities for detecting HSIL increased from 60.6 percent for a single biopsy to 85.6 percent for two biopsies to 95.6 percent for three biopsies.

**Conclusion**

Collection of additional lesion-directed biopsies during colposcopy increased detection of histologic HSIL, regardless of patient characteristics. Taking additional biopsies when multiple lesions are present should become the standard practice of colposcopic biopsy.

Wentzensen, et al, Nov. 2014

# Implementation of the boundary marking tool




In place

In preparation

**Goal:** To create a worldwide database of colposcopy images with annotations and outcomes

Slide used by permission of Dr. Nicholas Wentzensen, NCI/NIH/USA

- **So the Boundary Marking Tool did a good job at collecting image annotations…**
- **…but when any of these factors changed**
  - **Image set to be viewed**
  - **Regions to be marked and labeled**
  - **Data fields to be collected**
  - **Observers to annotate the images**
- **…a programmer and database administrator needed to be involved to make the necessary system changes.**

- Complex algorithms are not always essential to have significant impact.
- **User value goes up as dependency on computer specialists goes down.**
- Engineers need the basic vocabulary and concepts of their medical application domain; medical experts need to be able to interpret quantitative system output.
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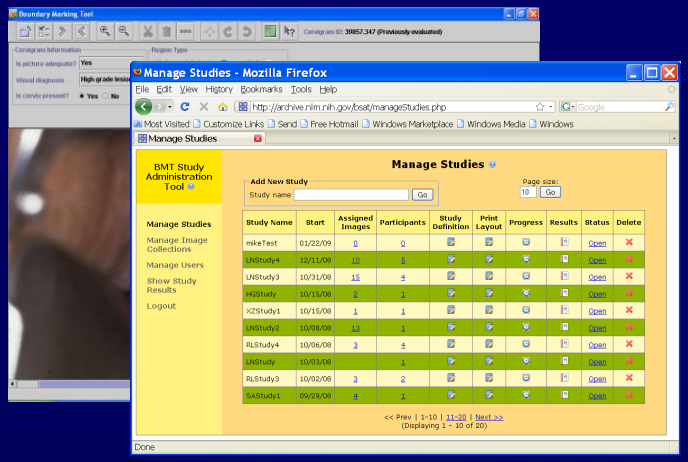
**Observations**

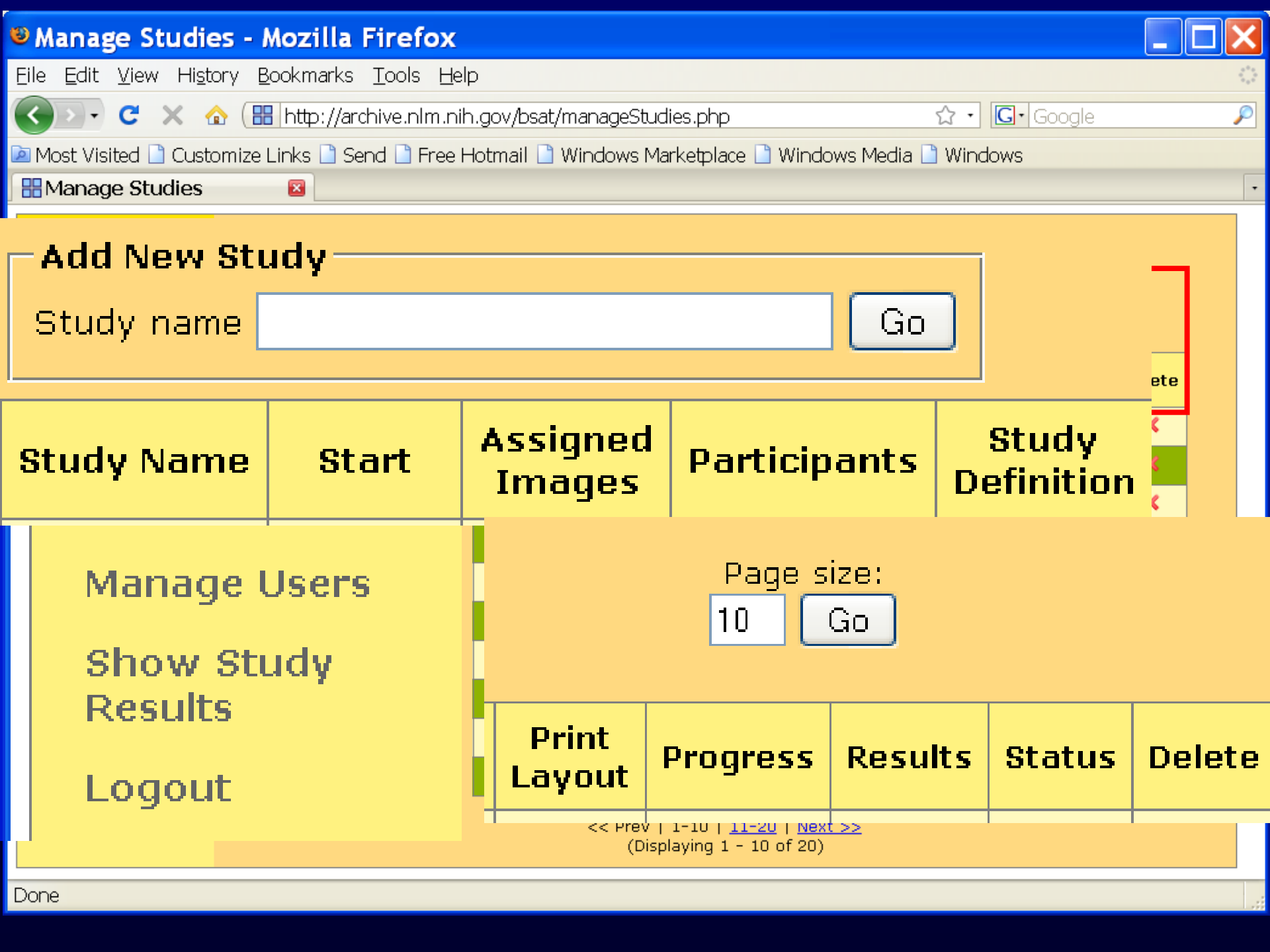



# BMT Study Administration Tool

## (BSAT, NLM/NIH ~2008)

- **BMT Study Administration Tool**
  - **Works with BMT**
  - **Allows a *user* to define a BMT study**
- **Components of BMT study:**
  - **Which images to use**
  - **Which graphical annotation to collect**
  - **Which observers will participate**

**Primary developer: Leif Neve**


Manage Studies - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://archive.nlm.nih.gov/bsat/manageStudies.php
Google
Most Visited Customize Links Send Free Hotmail Windows Marketplace Windows Media Windows
Manage Studies
Add New Study
Study name
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Study Name
Start
Assigned Images
Participants
Study Definition
Manage Users
Show Study Results
Logout
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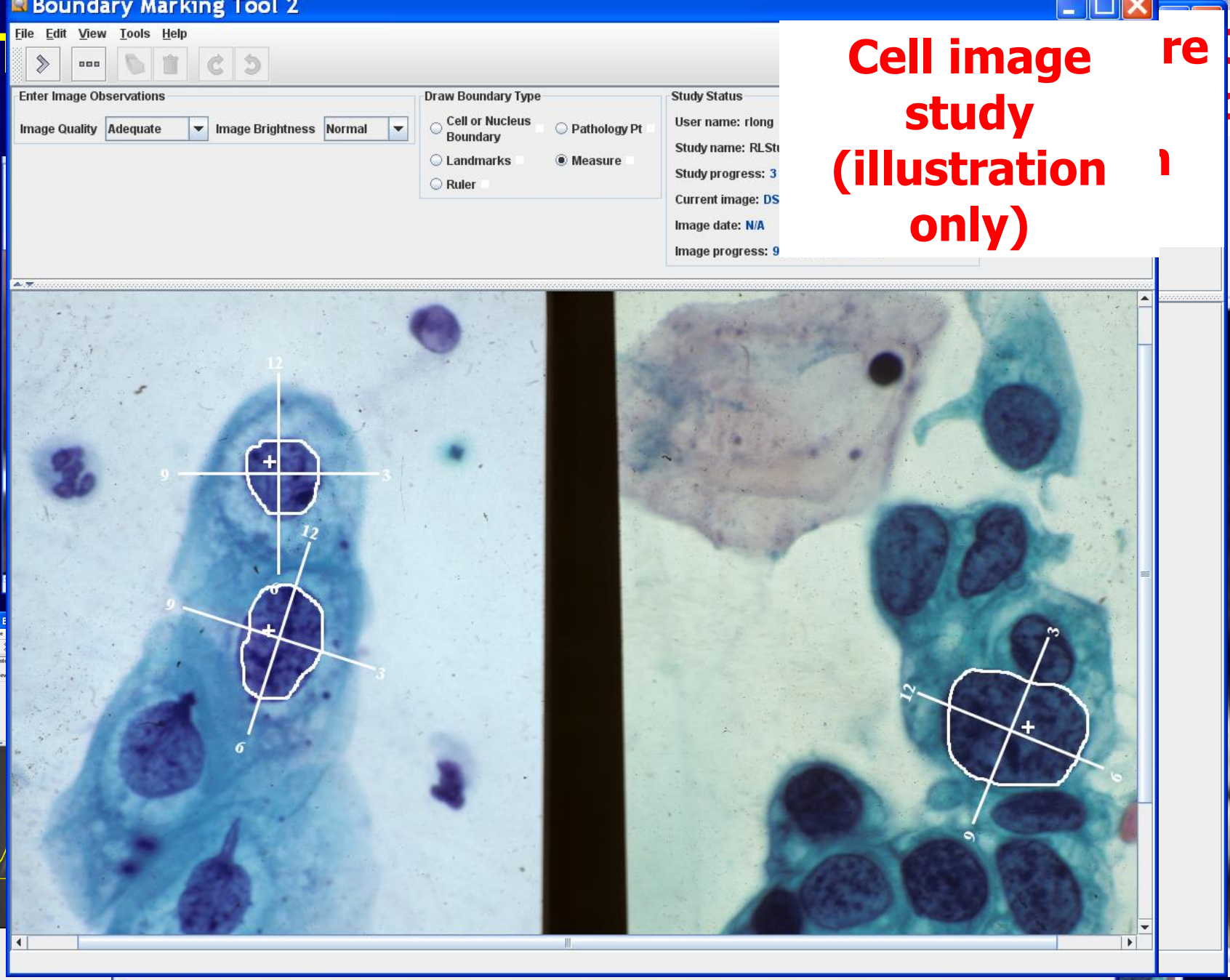
Boundary Marking Tool 2
File Edit View Tools Help
Enter Image Observations
Image Quality Adequate
Image Brightness Normal
Draw Boundary Type
Cell or Nucleus Boundary
Pathology Pt
Landmarks
Measure
Ruler
Study Status
User name: rlong
Study name: RLSt
Study progress: 3
Current image: DS
Image date: N/A
Image progress: 9
12
9
3
6
Cell image study (illustration only)

- Complex algorithms are not always essential to have significant impact.
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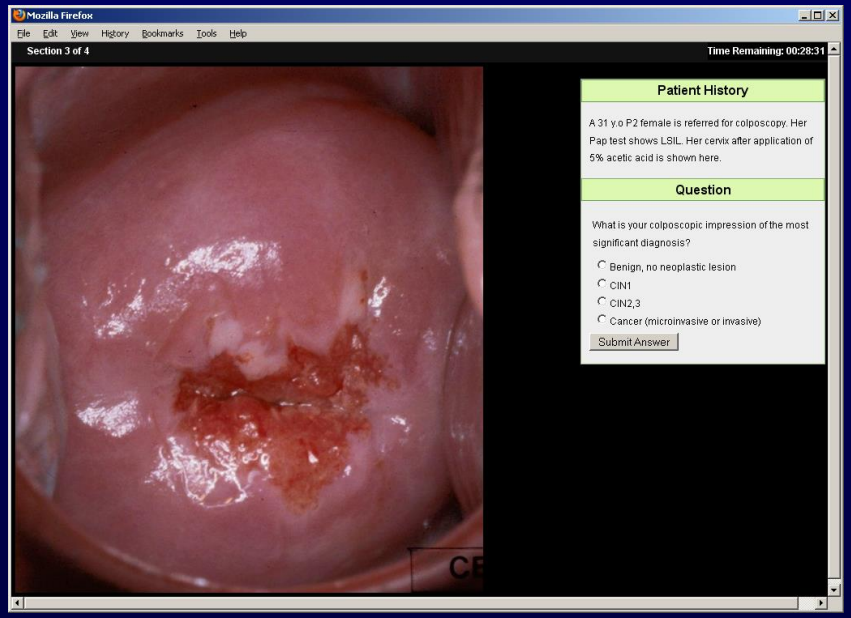
# The Teaching Tool
## (NLM/NIH ~2010)

- A system for collecting and scoring responses to image-based questions over the Web
- Current implementation is for field of *colposcopy*
  - Administers and grades two professional proficiency exams




Visual Diagnosis Question from TT

# Data for the Teaching Tool: Uterine Cervix Data

- Guanacaste
  - Costa Rica
  - 10,000 women
  - 7 years
  - Clinical data
    - PAP test, HPV, histology
  - Image data
    - 60,000 cervigrams
    - Histology images
    - PAP test images
- ALTS
  - United States
  - 2,000 women
  - 2 years
  - Clinical data
    - PAP test, HPV, histology
  - Image data
    - 40,000 cervigrams
    - Histology images
    - PAP test images

# Data for the Teaching Tool: Uterine Cervix Data

- Guanacaste
  - Costa Rica
  - 10,000 women
  - 7 years
  - Clinical data
    - PAP test, HPV, histology
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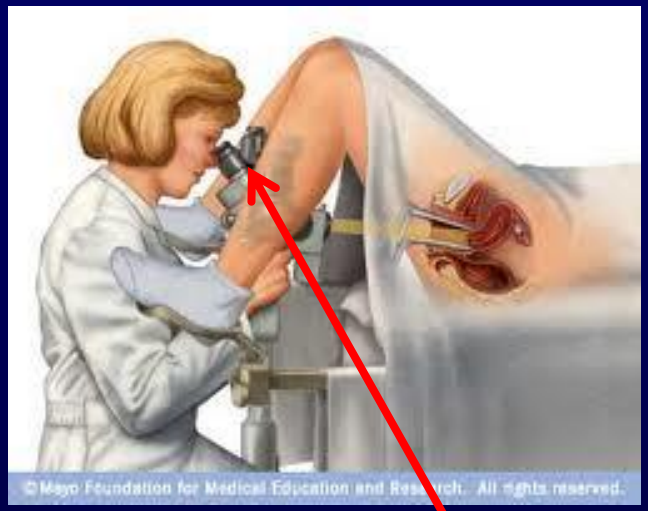
  - Image data
    - 40,000 cervigrams
    - Histology images
    - PAP test images


100,000 Digitized Uterine Cervix Images

# Colposcopy and NCI Cervigrams

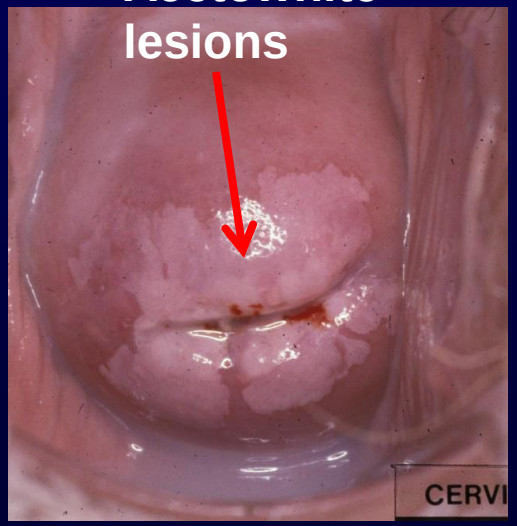
**Colposcopy[1]**




**Colposcopy image[2]**

**Acetowhite lesions**

**NCI Cervigram**




- **Cervix is treated with acetic acid, then viewed through a *colposcope***

- **Potentially diseased regions tend to turn whitish: "acetowhite lesions"**

[1]W7_colposcope.jpg / riversideonline.com

[2]105_f7.jpg / Aafp.org


ALTS cervigram

Pap test result

HPV test result

A 23 y.o. P1 female returns to your office for evaluation after her cervical cytology is reported as ASC-US with HPV DNA testing positive for high-risk types. Her cervix after application of 5% acetic acid is shown here.

The biopsy showed CIN1. Select one of the following as the most appropriate management option: [options follow]

Histology result

# Development with NCI and American Society for Colposcopy and Cervical Pathology (ASCCP)

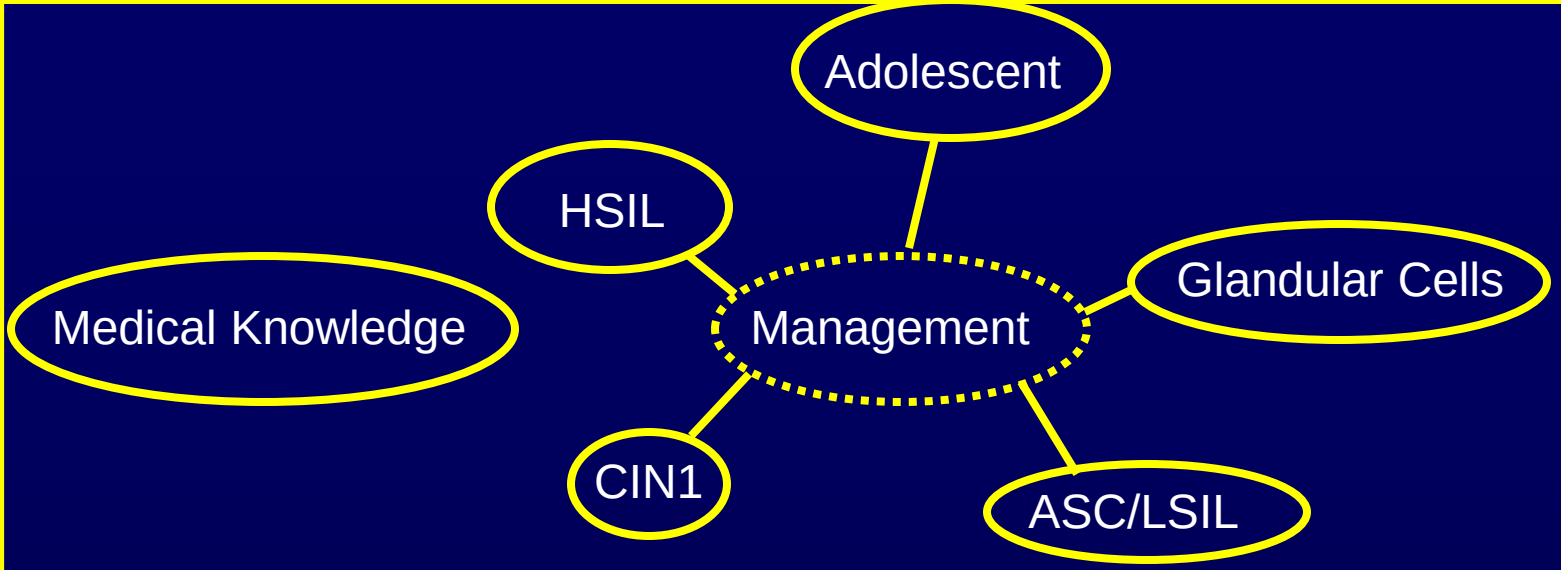
- Basic concepts
  - Operate on Web; image-based questions
  - Establish a database of exam content resources
    - "Pools" of questions and images of various categories
    - Create exams by drawing content from pools
- Question definition – medical experts
- "Where to biopsy?" questions required expert studies
  - Determine "correct" biopsy regions using BMT

# Dynamic Exam Creation

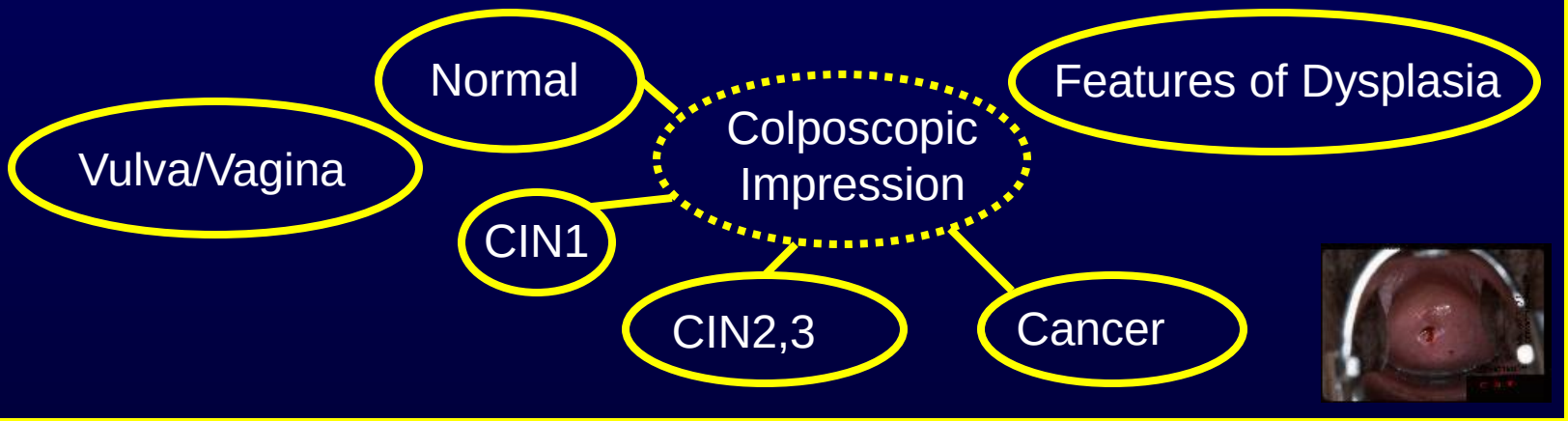
- Exams are dynamically “instantiated”
  - at time of user “Take Exam” request
- Questions are randomly drawn from pools

QUESTION POOLS

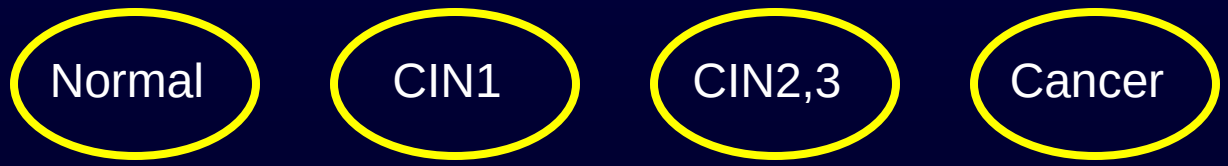
MULTIPLE CHOICE




SLIDE ID



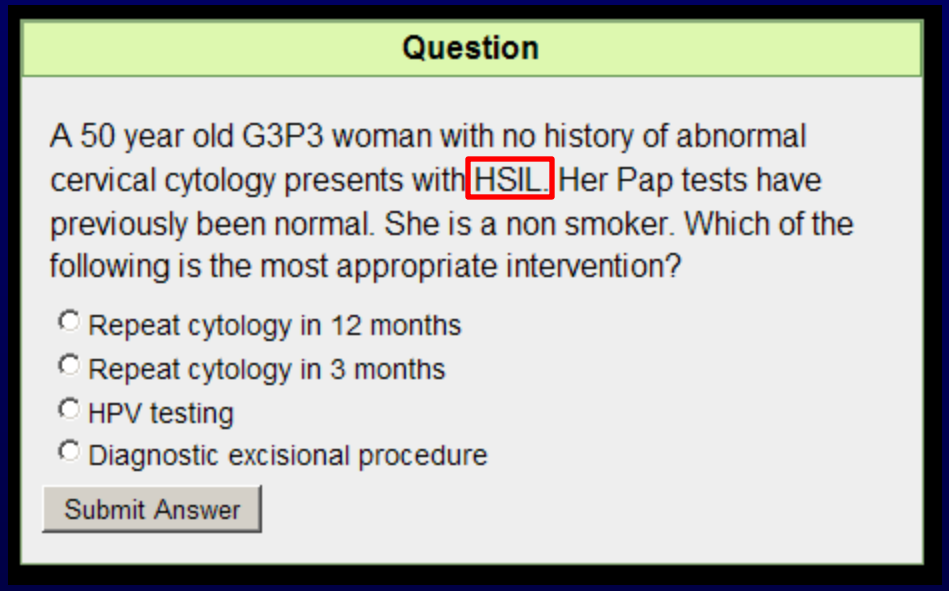

CASES




(DIAGNOSIS/BIOPSY/MANAGEMENT)

# Example Question
# Section: Multiple Choice
# Pool: Management of HSIL Pap Test

**H**igh-grade
**S**quamous
**I**ntraepithelial
**L**esion



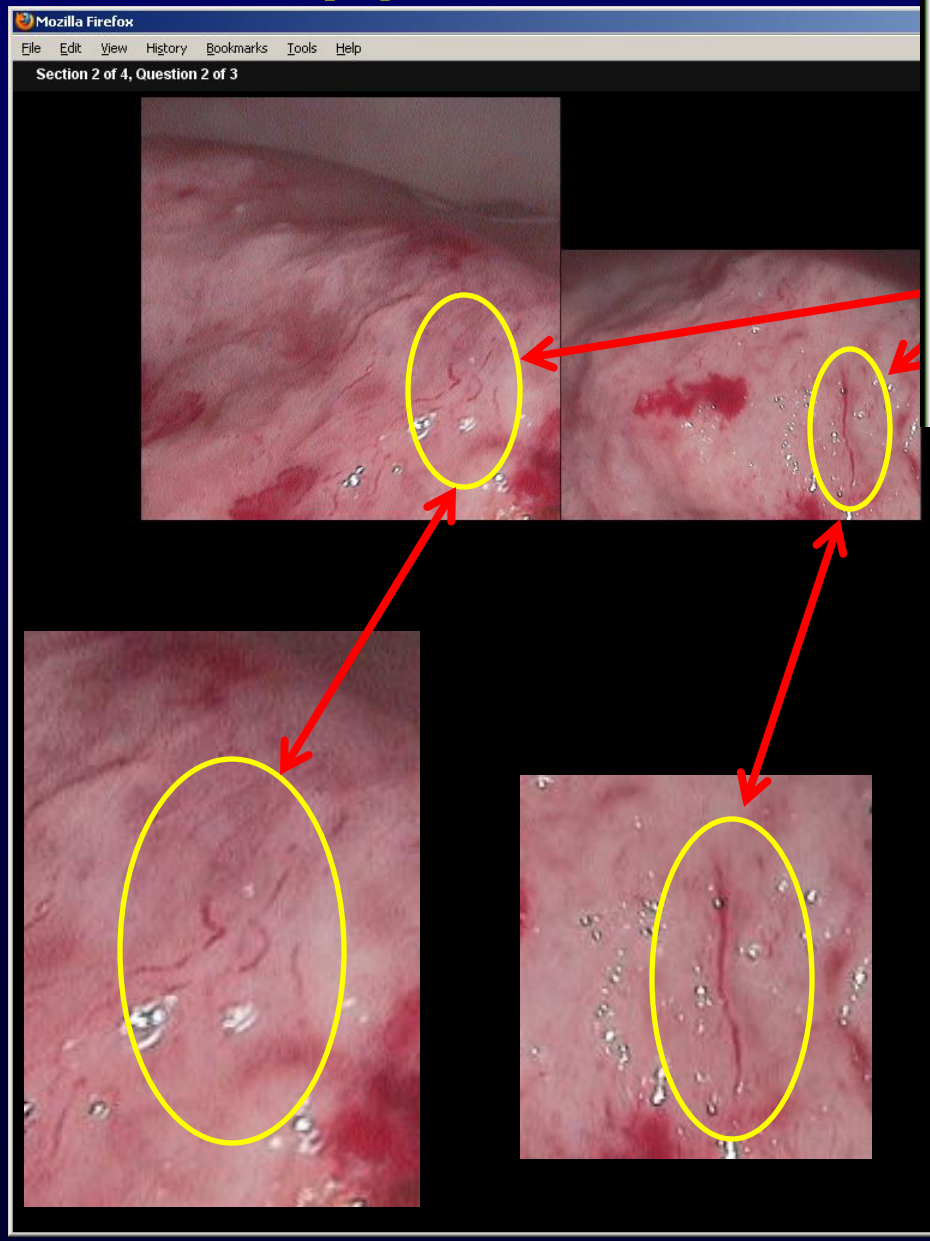

## Management by Pap test result

# Example Question

## Section: Slide ID

## Pool: Features of Dysplasia

Atypical Vessels




**Question**

Close-ups of two areas of the cervix are shown.

Which of these vascular patterns is seen?

- Arborizing (branching) vessels
- Punctation
- Mosaic
- Atypical vessels

Submit Answer

# Example Case
# Section: Cases
# Pool: HSIL by histology

- Three questions per case (one patient)
  - Diagnosis
  - Biopsy
  - Management

# Diagnosis…

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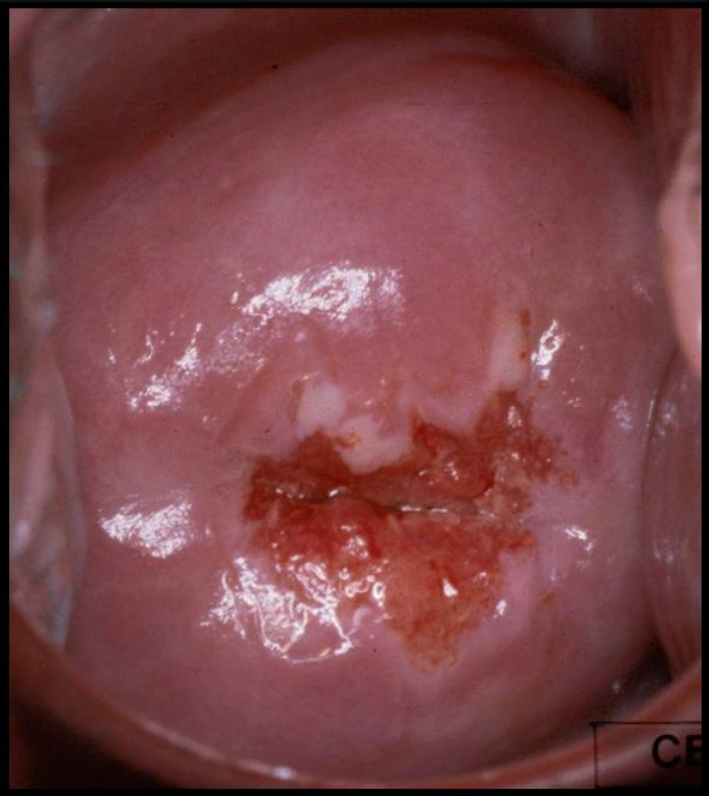
File Edit View History Bookmarks Tools Help

Section 3 of 4



## Patient History

A 31 y.o P2 female is referred for colposcopy. Her Pap test shows LSIL. Her cervix after application of 5% acetic acid is shown here.

## Question

What is your colposcopic impression of the most significant diagnosis?

- ○ Benign, no neoplastic lesion
- ○ CIN1
- ◉ CIN2,3
- ○ Cancer (microinvasive or invasive)

Submit Answer

# Some features considered in visual diagnosis

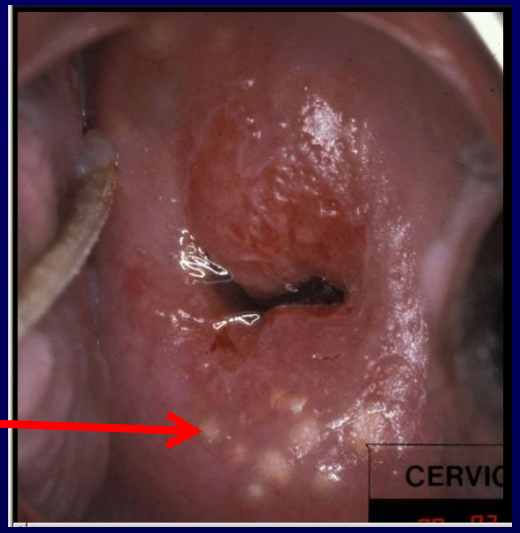
| Grade | Color | Vessel | Border | Surface |
|---|---|---|---|---|
| Benign | Pink, translucent | Fine, lacy | Nomal T zone | Flat |
| CIN 1 | Snowy white, shiny | None, fine PN, fine MO | Diffuse, feathery | Flat |
| CIN 2 | Whiter, shiny gray | None, PN, MO | Clearly demarcated | Flat, slightly raised |
| CIN 3 | Whitest, dull white, oyster white | None, coarse PN, coarse MO | Sharp, straight, demarcated, internal border | Raised |
| Microinvasive, invasive cancer | Red, yellow, dull gray | Atypical, irregular | Peeling, clearly demarcated, rolled edges | Nodular, ulcerated, necrotic, exophytic |

PN: punctation, MO: mosaicism

# Diagnosis Examples

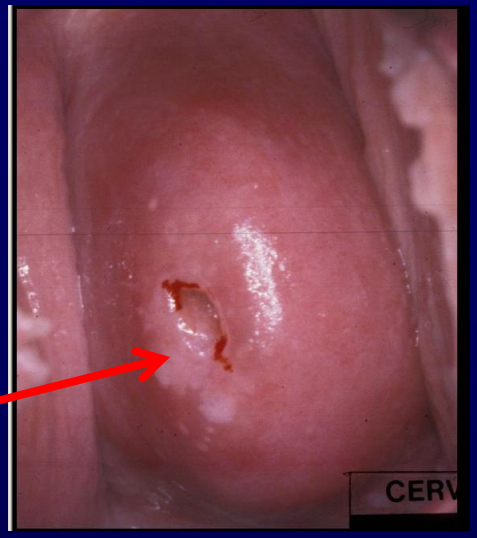
Benign

Cysts



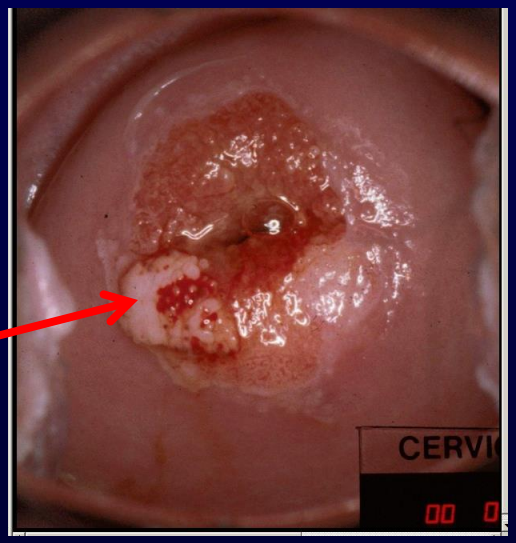
CIN 1

Aceto-white, flat, feather-edged



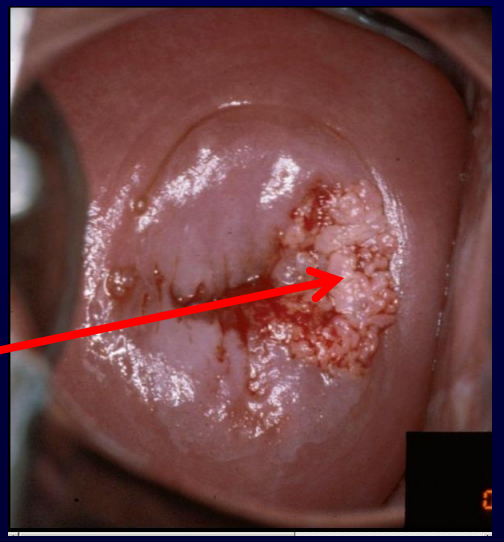
CIN 2,3

Acetowhite, demarcated, raised



Cancer

Possible exophytic tissue

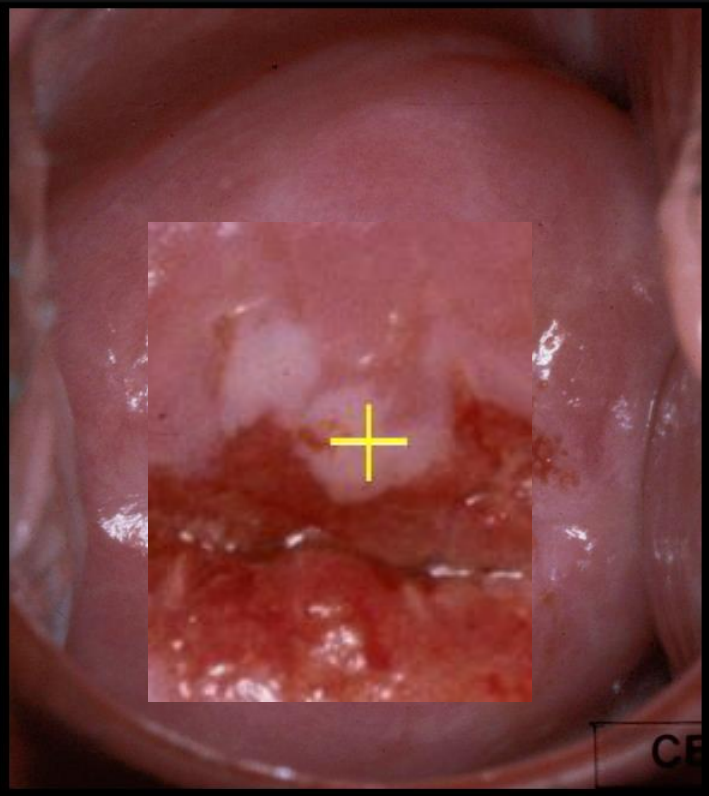


# Biopsy…

Mozilla Firefox

File Edit View History Bookmarks Tools Help

Section 3 of 4



## Patient History

A 31 y.o P2 female is referred for colposcopy. Her Pap test shows LSIL. Her cervix after application of 5% acetic acid is shown here.

## Question

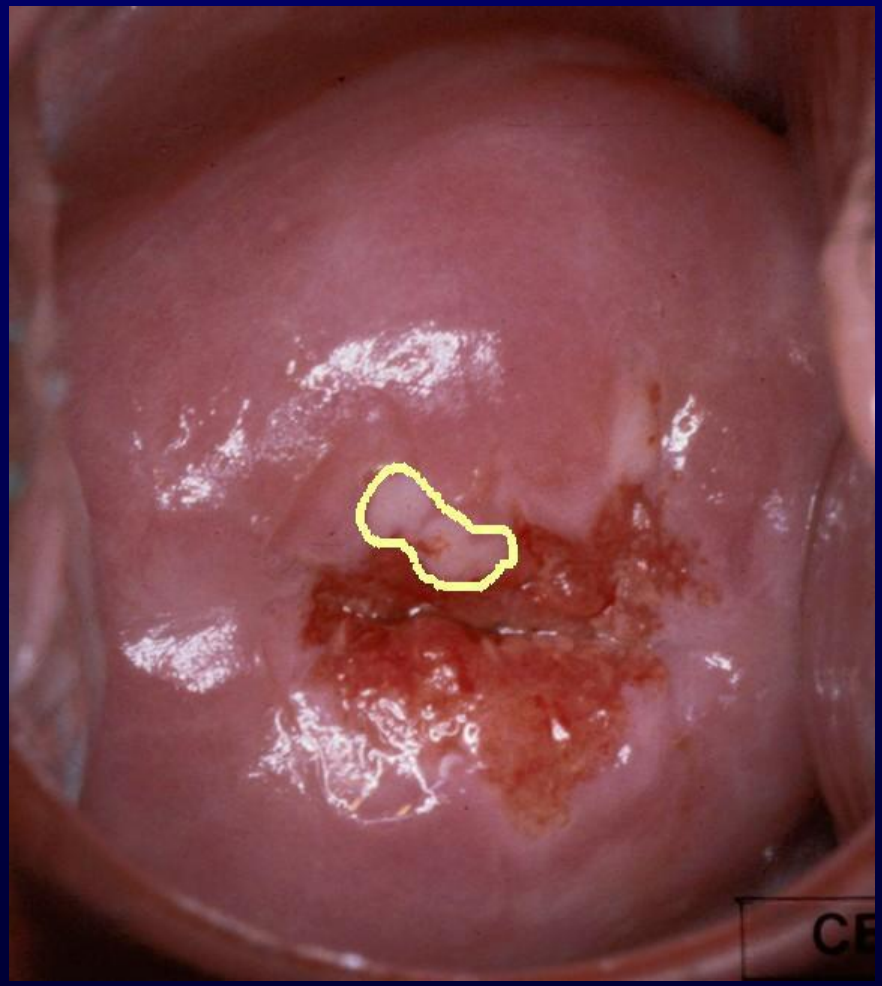
Use your computer's mouse to select the biopsy site that would best confirm your colposcopic impression. Move the mouse arrow to the location on the cervix where you would biopsy.
Double-click to select this spot; a crosshair will appear to indicate the location you have chosen. You may change your biopsy location by simply moving the mouse arrow and double-clicking at a new spot. If you would take no biopsy, check the box "No Biopsy Needed" below.

Assume that an endocervical curettage (ECC), if done, is negative for dysplasia.

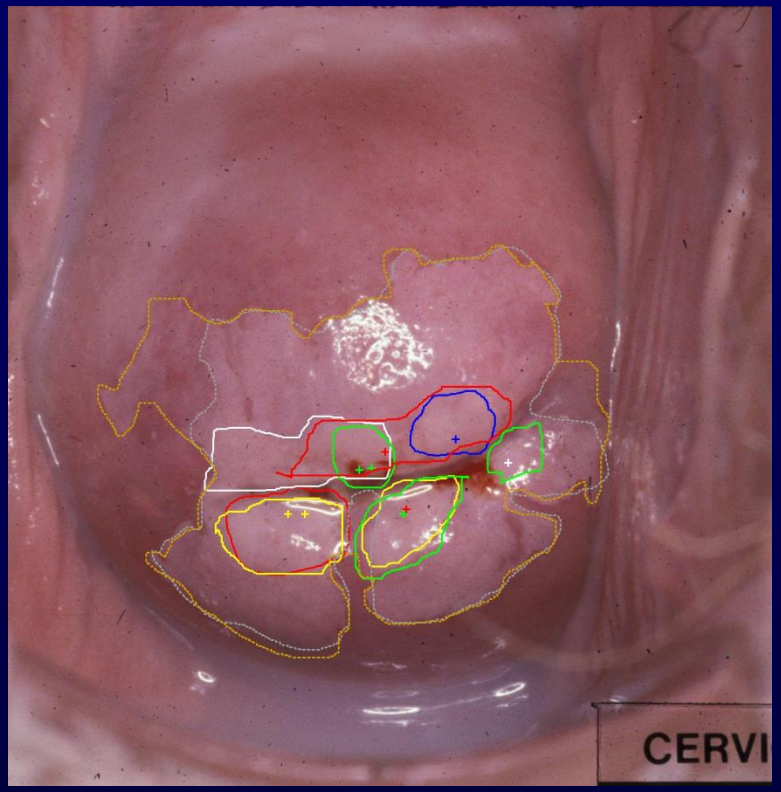
☐ No Biopsy Needed (Marks on images ignored and reset if this is selected)

Submit Answer

# Acceptable biopsy region…

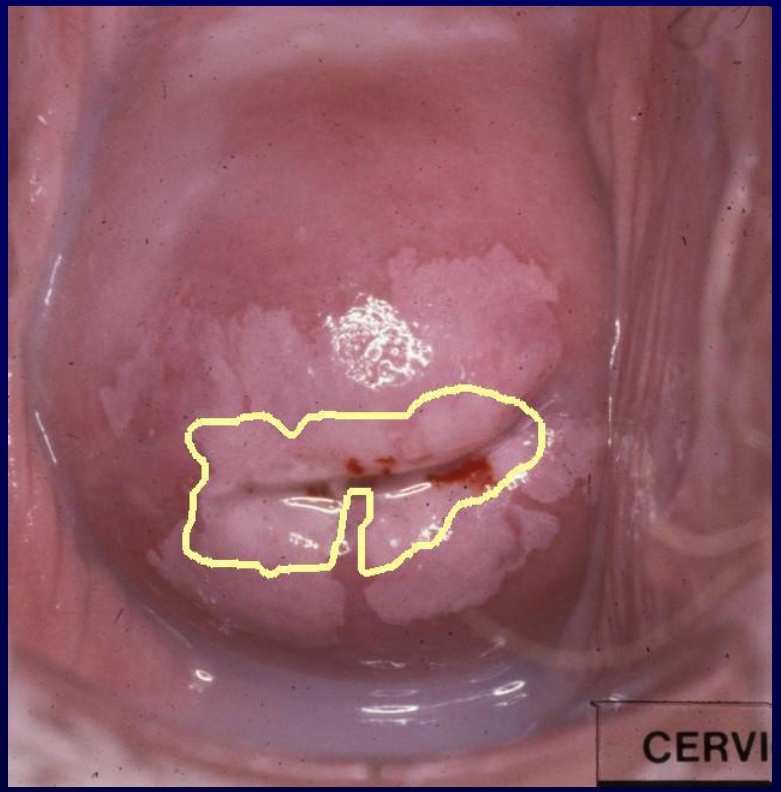


# What is “correct” biopsy region?




5 expert opinions

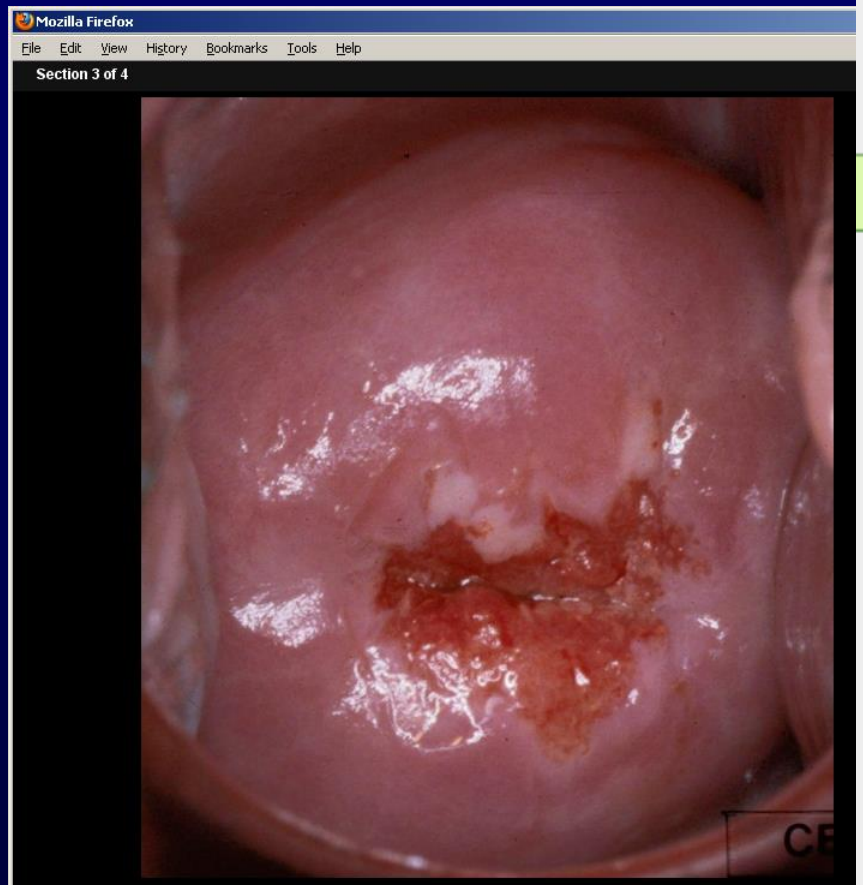
1 2 3 4 5




5 expert opinions

Consensus

# Management…




## Patient History

A 31 y.o P2 female is referred for colposcopy. Her Pap test shows LSIL. Her cervix after application of 5% acetic acid is shown here.

## Question

The biopsy showed CIN2,3. According to the most recent ASCCP Guidelines, which of the following is the most appropriate management option?

- ○ Repeat cytology in 12 months
- ○ Repeat cytology in 6 and 12 months or HPV DNA testing in 12 months
- ○ Treat or observe with cytology and colposcopy at 6 month intervals for up to 24 months
- ◉ Excision of the transformation zone

Submit Answer

# Current System Usage

- Two ASCCP Exams implemented
  - Residents' Online Exam (ROE)
    - Taken by residents in Ob/Gyn or Family Practice programs
  - Colposcopy Mentorship Program exam (CMP)
    - More advanced; taken in post-residency
- Includes Practice Exam, reporting, admin functions
- Went operational May 2010
- 133 resident programs, 2701 exams taken, 3286 total users
- Runs on ASCCP server in Amazon cloud

| ID | Institution | Practice Setting | | | | |
|---|---|---|---|---|---|---|
| 1 | University of Colorado Obstetrics and Gynecology Residency Training Program | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 2 | The University of Texas Southwestern Medical Center at Dallas | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 3 | University of New Mexico School of Medicine OB/GYN Residency Program | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 4 | George Washington University | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 5 | University of Oklahoma Health Sciences Center | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 6 | Stamford Hospital, Columbia University | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 7 | University of Virginia Health System | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 8 | Texas Tech University Health Sciences Center | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 9 | The Methodist Hospital - Houston | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 10 | Henry Ford Hospital Family Medicine Residency Program | Family Practice | Edit | Add Resident | Show Residents | Paid Exams |
| 11 | Washington University School of Medicine | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |
| 12 | Baylor College of Medicine | Ob/Gyn | Edit | Add Resident | Show Residents | Paid Exams |


10 Henry Ford Hospital Family Medicine Residency Program Family Practice Edit Add Resident Show Residents Paid Exams
11 Washington University School of Medicine Ob/Gyn Edit Add Resident Show Residents Paid Exams
12 Baylor College of Medicine Ob/Gyn Edit Add Resident Show Residents Paid Exams

# Example Report: CMP Exam

ASCCP Colposcopy Mentorship Program Exam
Performance Report

Name: Long, Rodney

Possible Points: 119.50
Score: 111.25

You must pass each of the three assessment areas to meet the requirements of the CMP. The results of your exam are shown below.

| Assessment Area | Points Possible | Points Required | Score | |
|---|---|---|---|---|
| Medical Knowledge | 70 | 52 | 64 | ✓ |
| Colposcopy ID and Cases | 49.5 | 36.75 | 47.25 | ✓ |
| | No. Questions | No. Required | No. Correct | |
| Biopsy Placement | 12 | 10 | 12 | ✓ |

Congratulations, you have met the requirements for the CMP

The following page has a breakdown of your performance by skills and knowledge assessed. Please consider it a reference and guide during your continuing education.

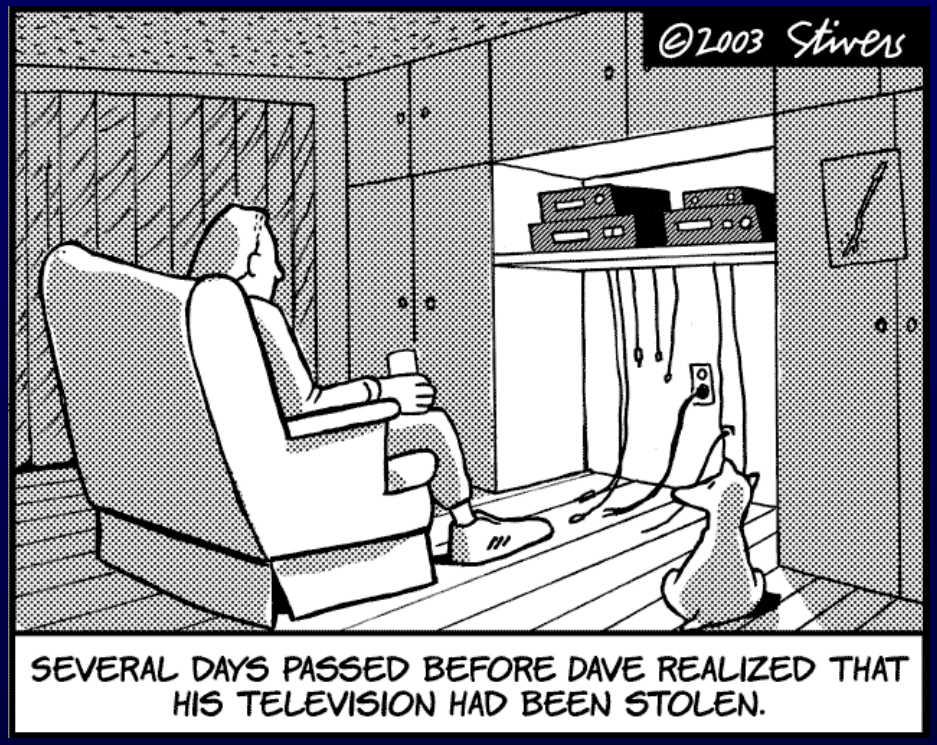


| Medical Knowledge | No. Questions | No. Correct | % Correct |
|---|---|---|---|
| medical knowledge | 17 | 17 | 100 |
| **Management** | **No. Questions** | **No. Correct** | **No. Correct** |
| management, adolescent | 3 | 3 | 100 |
| management, HSIL | 5 | 5 | 100 |
| management, glandular cells | 2 | 2 | 100 |
| management, ASC/LSIL | 6 | 5 | 83.3 |
| management, CIN 1 | 2 | 0 | 0 |
| **Colposcopy ID/Pattern Recognition** | **No. Questions** | **No. Correct** | **% Correct** |
| colposcopic impression, normal | 2 | 2 | 100 |
| colposcopic impression, LSIL | 2 | 2 | 100 |
| colposcopic impression, HSIL | 3 | 3 | 100 |
| colposcopic impression, cancer | 2 | 2 | 100 |
| vulva-vagina | 3 | 3 | 100 |
| features of dysplasia | 3 | 3 | 100 |
| **Cases** | **No. Questions** | **No. Correct** | **% Correct** |
| diagnosis (pattern recognition) | 12 | 10 | 83.3 |
| biopsy placement | 12 | 12 | 100 |
| management | 12 | 11 | 91.7 |
| **Exam Summary** | **No. Questions** | **No. Correct** | **% Correct** |
| medical knowledge | 17 | 17 | 100 |
| pattern recognition | 27 | 25 | 92.6 |
| biopsy placement | 12 | 12 | 100 |
| management | 30 | 26 | 86.7 |

–Diagnosis / Pattern Recognition: Images or lesion descriptions that ask for a diagnosis
–Management: Images, lesion descriptions, or questions that essentially ask, "How would you manage this patient?"
–Biopsy placement: Image-based questions that require the test taker to indicate where on the image they would take a biopsy.
–Medical knowledge: Questions of a more general nature, including questions about diagnosis or management options but that don't specifically ask for a diagnosis or specific management plan.

# But Something's Missing…

- The system clearly reports how test-takers are performing…
- …it could also report on how the questions themselves are performing.



# IDEA

**Quantitative question analysis may help us identify questions**

- **which are poorly constructed, or**

- **where we should focus on better Resident training.**

**This may be high-value capability to incorporate into the system.**

# Teaching Tool Data Analyzed

- Collection Period: May 2010–May 2012
- 830 Resident (ROE) Exams
- 830 x 74 = 61,420 responses graded

# Methods

- "Standard" analysis methods
  - Per cent correct by question
  - Per cent responses for each question option
  - Point biserial correlation by question

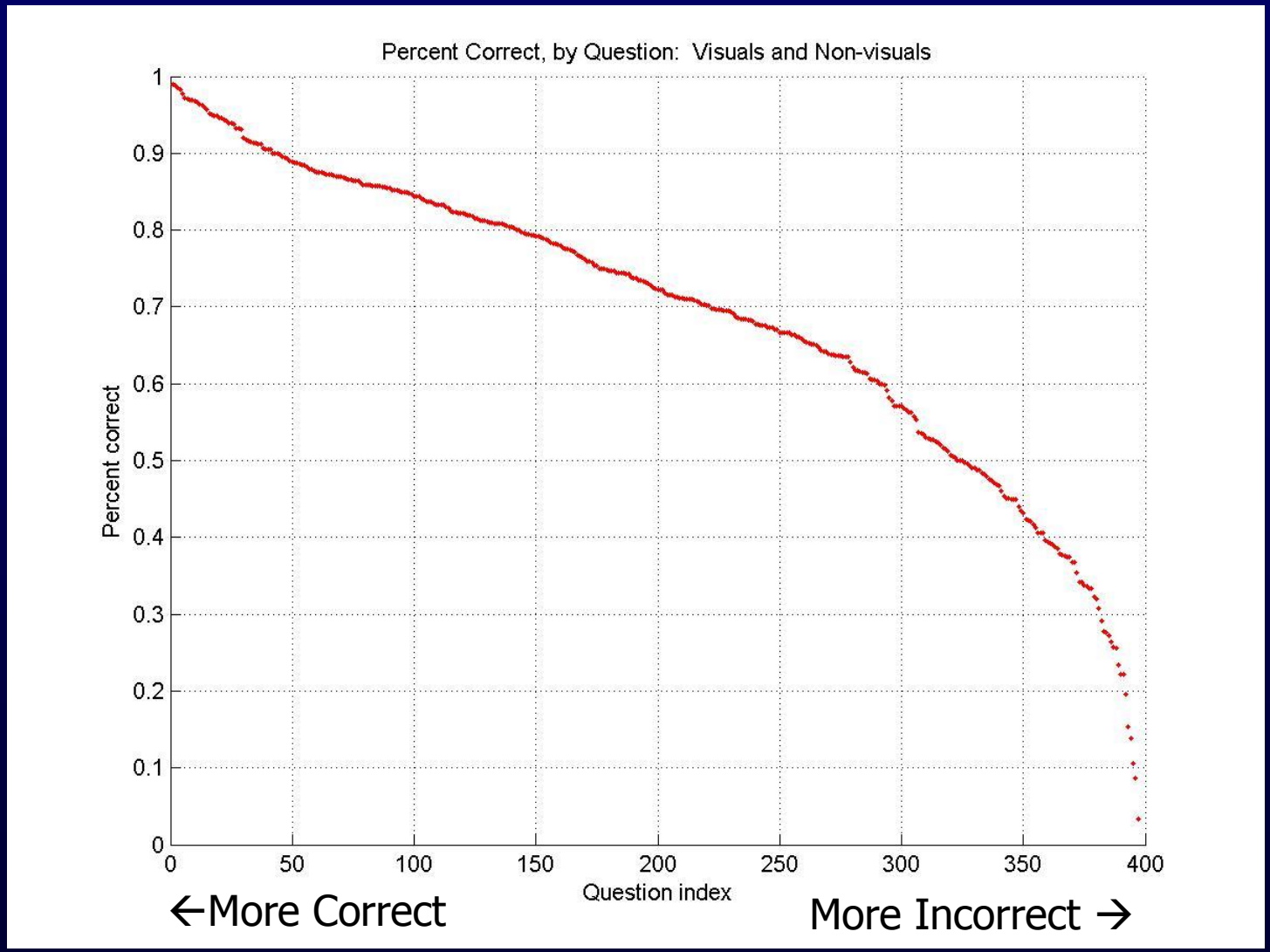
- Unique methods
  - Spatial characteristics of biopsy placement

# Methods

- "Standard" analysis methods
  - Per cent correct by question
  - Per cent responses for each question option
  - Point biserial correlation by question

- Unique methods
  - Spatial characteristics of biopsy placement

# Percent Correct by Question



# Lowest Quartile Correct Responses

| Ques Num | Frac Correct | N Ques |
|---|---|---|
| 110 | 0.03 | 60 |
| 170 | 0.09 | 93 |
| 287 | 0.11 | 235 |
| 89 | 0.14 | 58 |
| 398 | 0.15 | 104 |
| 221 | 0.20 | 102 |
| 235 | 0.22 | 90 |
| 106 | 0.22 | 45 |
| 55 | 0.23 | 619 |

# Question 110

**Based on the appearance of this cervix after application of 5% acetic acid, what is your colposcopic impression of the most significant diagnosis?**

| Benign, no neoplastic lesion | CIN1 | CIN2,3 | Cancer (microinvasive or invasive) |
|---|---|---|---|
| .20 | .03 | .1 | .67 |

**N = 60**

# Question 170

**A 31 y.o P2 female is referred for colposcopy. Her Pap test shows LSIL. Her cervix after application of 5% acetic acid is shown here. What is your colposcopic impression of the most significant diagnosis?**


| Benign, no neoplastic lesion | CIN1 | CIN2,3 | Cancer (microinvasive or invasive) |
|---|---|---|---|
| .14 | .77 | .09 | 0 |

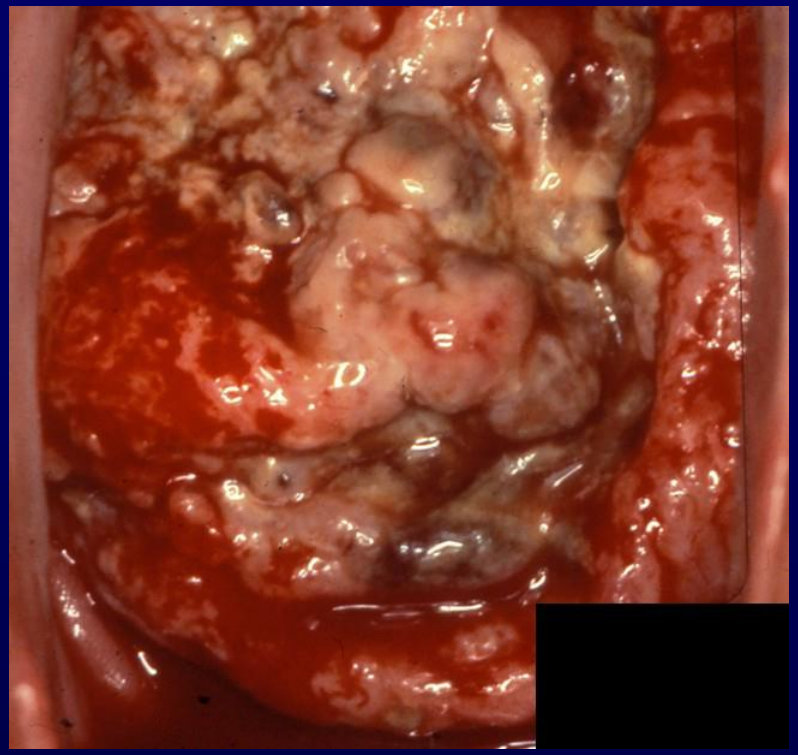
**N = 93**

# Highest Quartile Correct Responses: 178 questions; top 5 shown

| Ques Num | Frac Correct | N Ques |
|---|---|---|
| 499 | 0.99 | 197 |
| 216 | 0.99 | 86 |
| 438 | 0.99 | 344 |
| 44 | 0.98 | 173 |
| 444 | 0.97 | 314 |

# Question 499

**Based on the appearance of this cervix after application of 5% acetic acid, what is your colposcopic impression of the most significant diagnosis?**



| Benign, no neoplastic lesion | CIN 1 | CIN 2,3 | Cancer (microinvasive or invasive) |
|---|---|---|---|
| 0 | .005 | .005 | .99 |

**N = 199**

# Question 44

**The magnified inset from the anterior lip of this cervix shows which of these vascular patterns?**

| Arborizing (branching) vessels | Punctation | Mosaic | Atypical vessels |
|---|---|---|---|
| .01 | .98 | .01 | 0 |

**N = 173**

# Methods

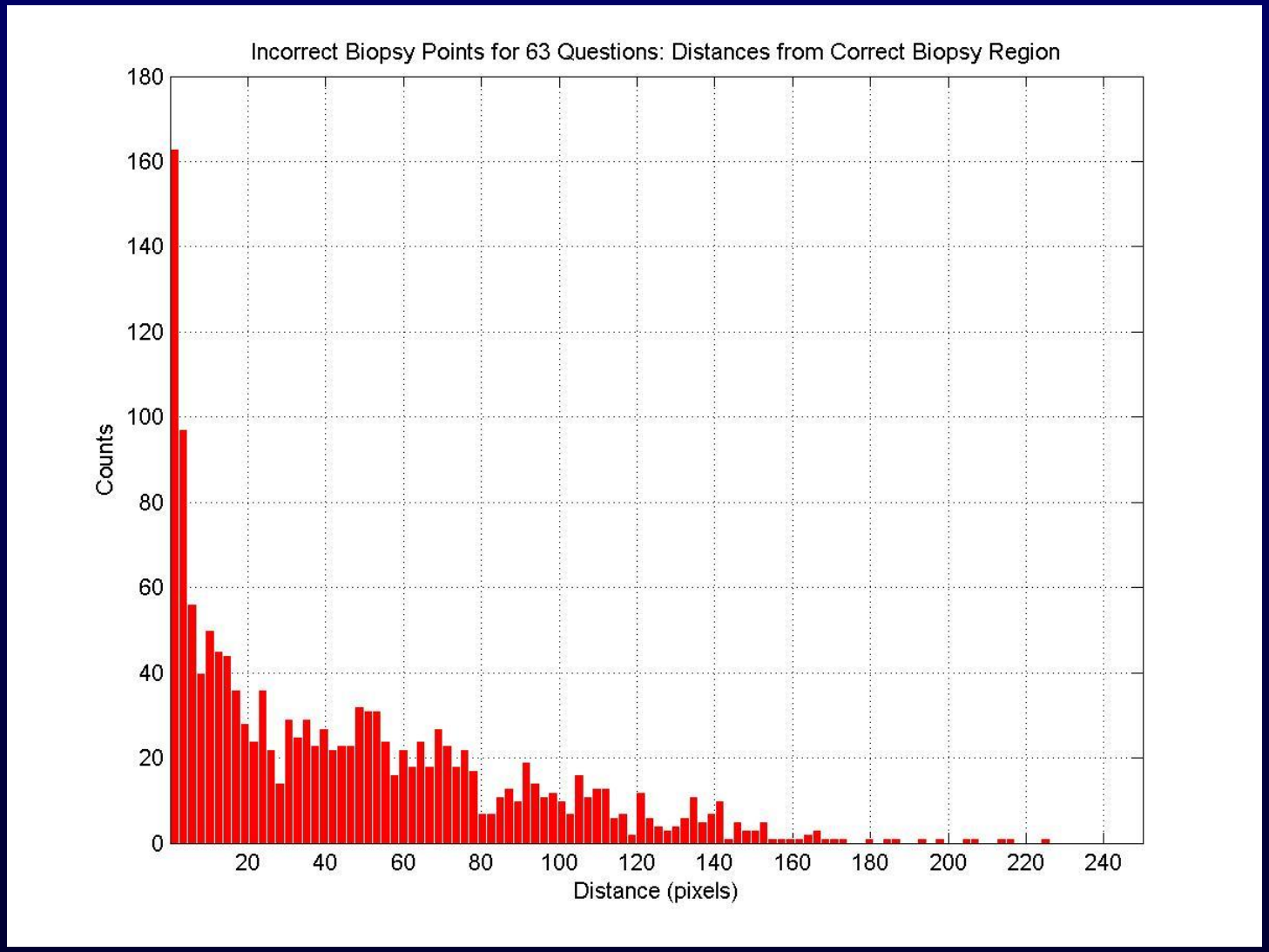
- "Standard" analysis methods
  - Per cent correct by question
  - Per cent responses for each question option
  - Point biserial correlation by question

- Unique methods
  - Spatial characteristics of biopsy placement

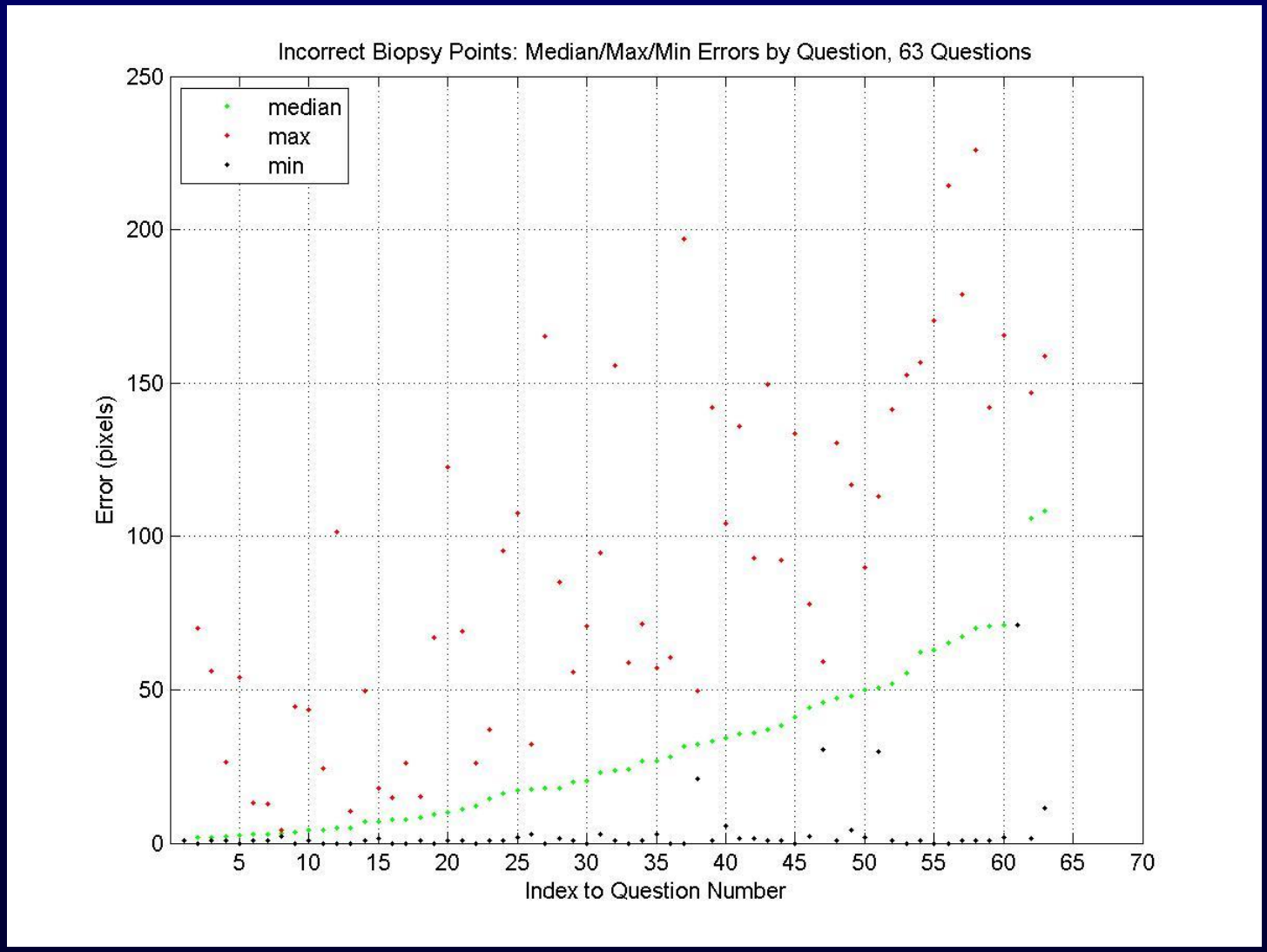
# Biopsy Questions

- **Spatial analysis: not in the standard test analysis methods**

- **How far are incorrect biopsy points from the correct answer?**


Incorrect Biopsy Points for 63 Questions: Distances from Correct Biopsy Region
Counts
Distance (pixels)
0
20
40
60
80
100
120
140
160
180
200
220
240

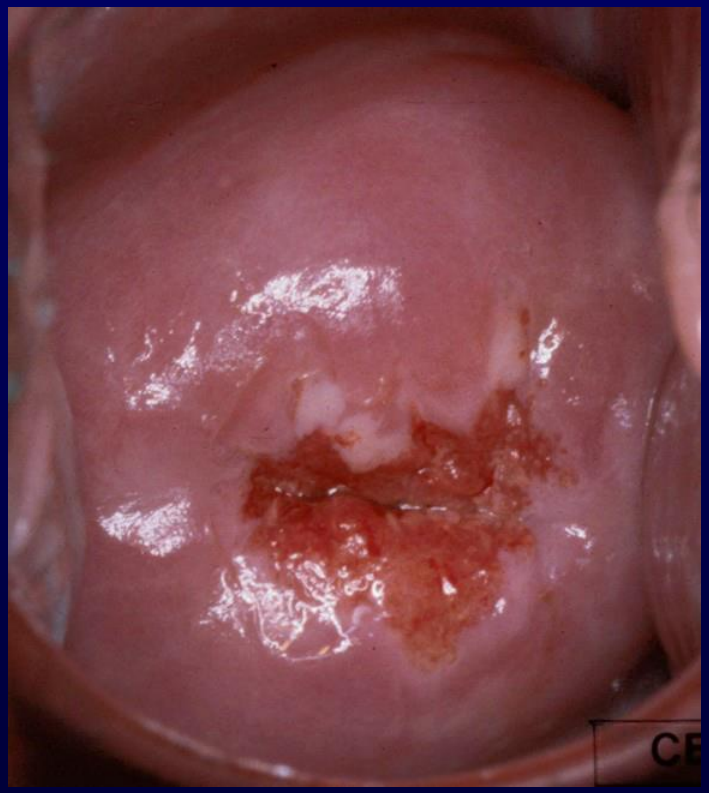
# Biopsy Errors by Question, Ranked by Median Error



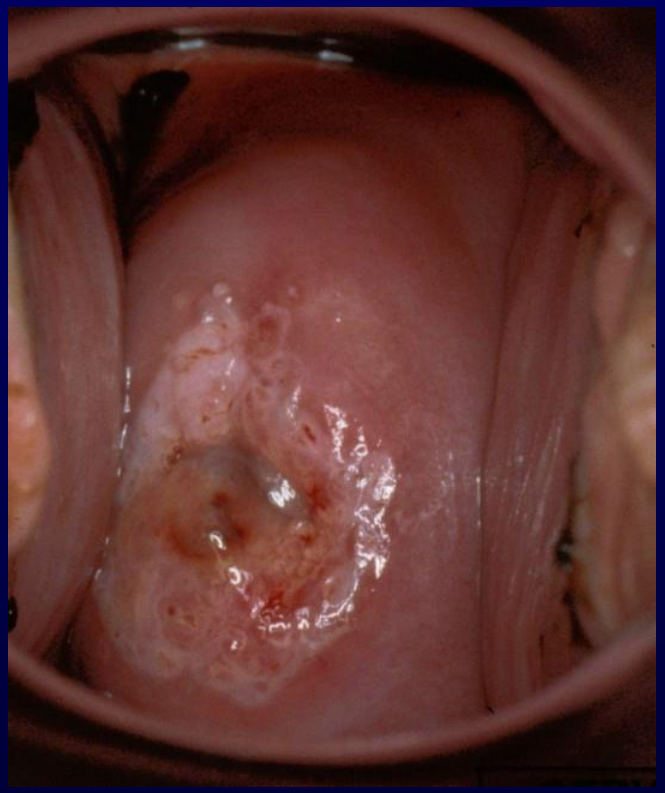
# Questions with Highest Median Errors in Biopsy Placement

| Ques Num | Median Dist to Correct Boundary (Pix) | Num Incorrect Biop Pts | Total Biop Pts |
|---|---|---|---|
| 150 | 108 | 21 | 109 |
| 384 | 106 | 55 | 102 |
| 270 | 71 | 1 | 99 |
| 213 | 71 | 45 | 101 |
| 333 | 71 | 102 | 223 |
| 372 | 70 | 27 | 112 |
| 381 | 67 | 72 | 120 |
| 165 | 65 | 80 | 205 |
| 159 | 63 | 65 | 106 |

# Questions with High Biopsy Placement Error



150



384

- Complex algorithms are not always essential to have significant impact.
- User value goes up as dependency on computer specialists goes down.
- Engineers need the basic vocabulary and concepts of their medical application domain; medical experts need to be able to interpret quantitative system output.
- **Small systems have a natural fit for problem-solving in low-resource areas.**
- Advanced algorithms may provide critical assistance to the clinician, but workflow can be a showstopper.
- Attention to error and failure modes may yield the biggest payoff in building practical systems.

**Observations**

# The Visual Triage Tool
## (NLM/NIH ~2007)

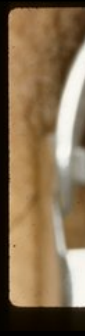
NCI Visual Triage Study - Mozilla Fire

File Edit View Go Bookmarks Tools Help

http://archive/ncivisualtriag

Customize Links Free Hotmail Windows Marketp

Tiempo: 00:04:20



**Edad:** 28

1)Es la imagen adecuada para la evaluación?

- Sí
- No

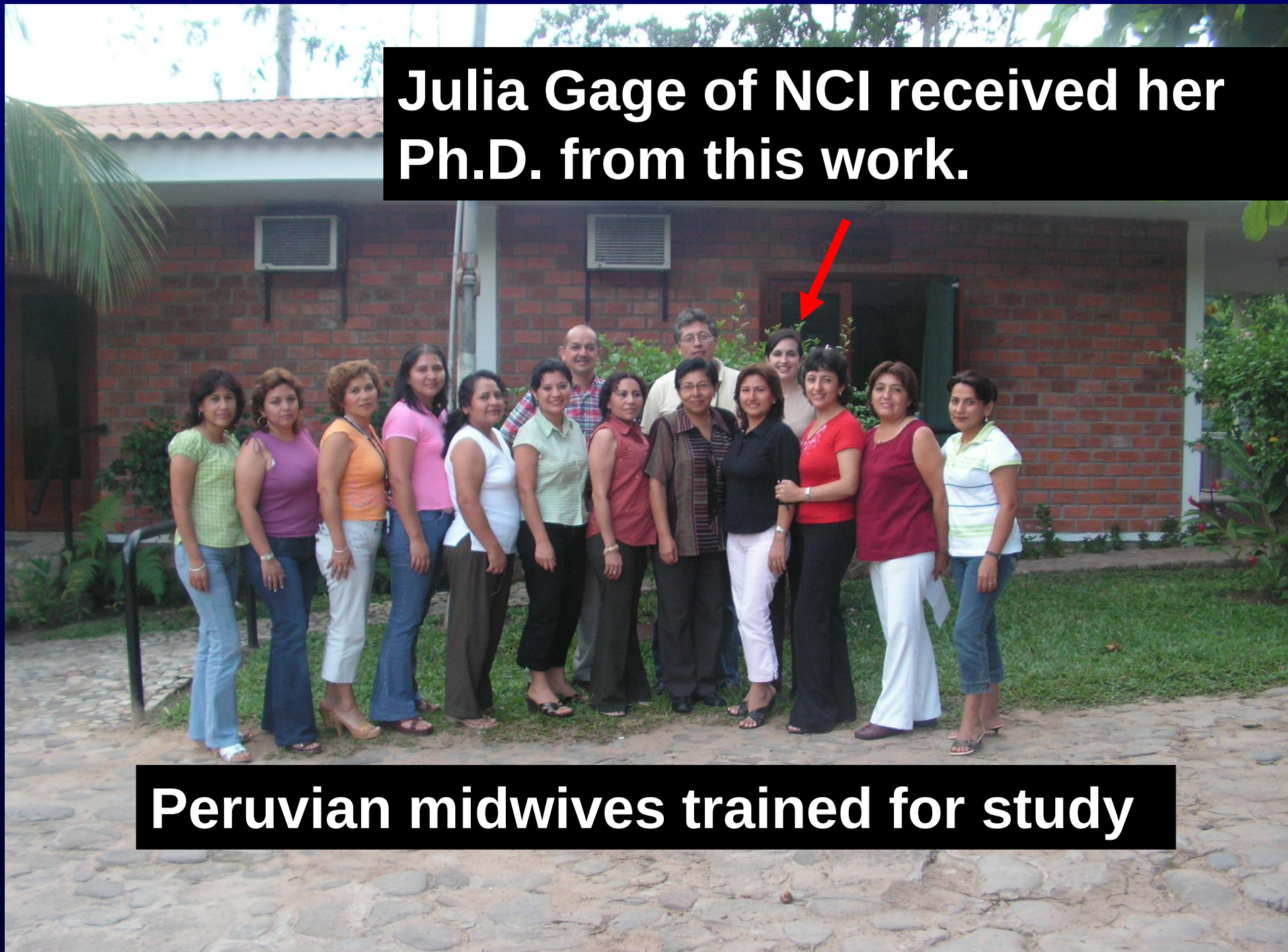
# Study Question: How well can trained non-experts screen HPV-positive women for treatment by cryotherapy?

**Screen image sized to simulate cervix view in practice**

- Ectopia muy grande
- Pared vaginal muy cerca al cérvix

**Visual Triage Study Tool**


Moyobamba
Tarapoto
amarca
0°
78°
72°
Quito
Napo R
Colombia
Caqueta R
Manta
Ecuador
Ambato
Pastaza R
Putumayo R
Japurá R
Guayaquil
Cuenca
Amazonas R
Tumbes
Peru
Iquitos
Loja
Javari R
Benjamin Constant
Talara
Sullana
Piura
Marañón R
Ucayali R
Brazil
Paita
Chachapoyas
Moyobamba
Juruá R
Chiclayo
Tarapoto
Cajamarca
Cruzeiro
Huallaga R
Trujillo
Pucallpa
Salaverry
Marañón R
Tingo
Purús R
Chimbote
María
Huaráz
Huánuco
Pacific
Ocean
Urubamba R
Purús R
Goyllarisquizga
Cerro de Pasco
Cobija
Huacho
Lima
Madre de Dios R
12°
Callao
Huancayo
Puerto
Huancavelica
Ayacucho
Maldonado
Pisco
Abancay
Cuzco
Ica
Apurímac R
Nazca
Lago
Titicaca
Bo-
livia
Puno
0
300 km
0
200 mi
Arequipa
La
Paz
Moquegua
Desaguadero R
Tacha
Arica
Chile
18°
©1997 MAGELLAN Geographix℠
(805) 685-3100 www.maps.com


Julia Gage of NCI received her Ph.D. from this work.
Peruvian midwives trained for study

**An Evaluation of Visual Triage of Human Papillomavirus-Positive Women.**

***Ph.D. dissertation,*** **Johns Hopkins Univ. Bloomberg School of Public Health, 2008.**

**An Evaluation by Midwives and Gynecologists of Treatability of Cervical Lesions by Cryotherapy among Human Papillomavirus-Positive Women.**
***International Journal of Gynecological Cancer,*** **2009; 19(4):728-33.**

**Treatability by Cryotherapy in a Screen-and-Treat Strategy.**
***Journal of Lower Genital Tract Disease*****, 2009; 13(3), 174-181.**

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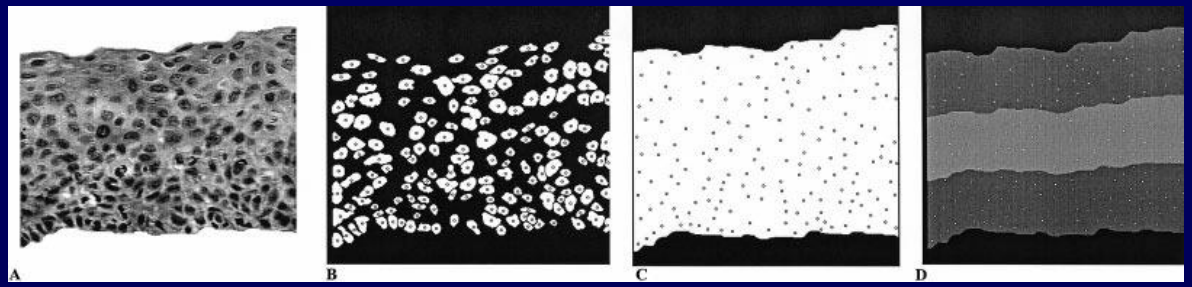
- **Advanced algorithms may provide critical assistance to the clinician, but workflow can be a showstopper.**
- Attention to error and failure modes may yield the biggest payoff in building practical systems.

**Observations**

# Disease Classification in Uterine Cervix Histology Images (NLM/NIH ~2012-present)

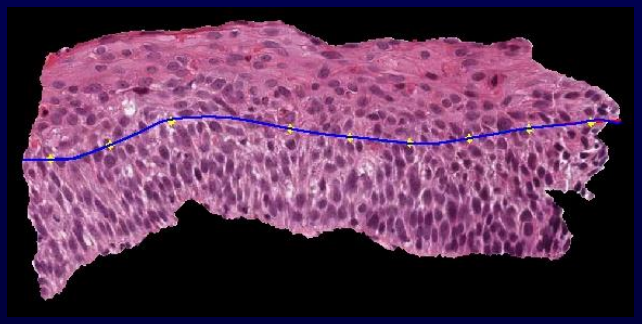



Epithelium image

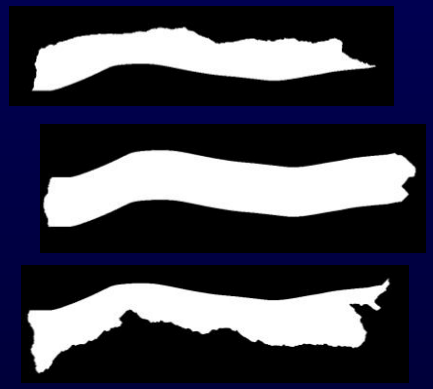
Detected nuclei

Nuclei centers

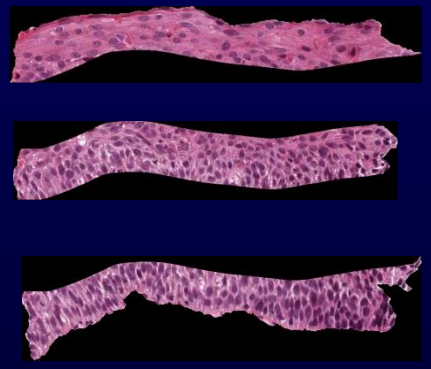
Analyze by layers



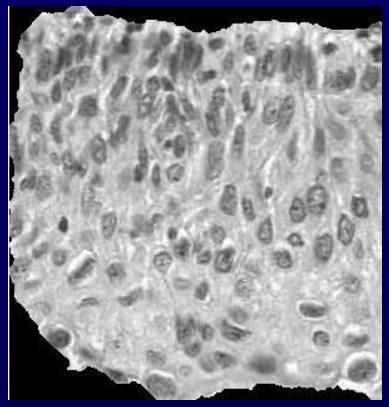
Find medial axis



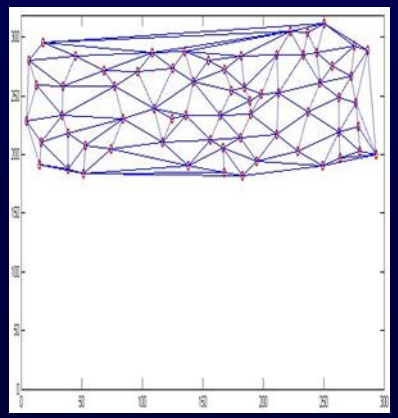
Compute layer masks



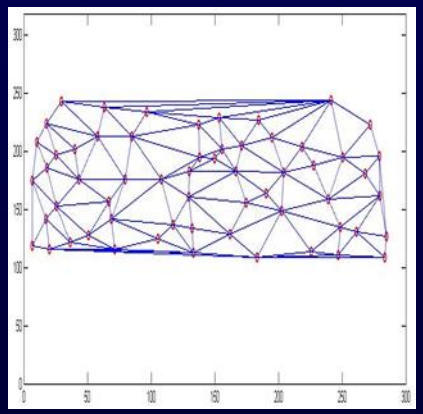
Apply masks to get image layers



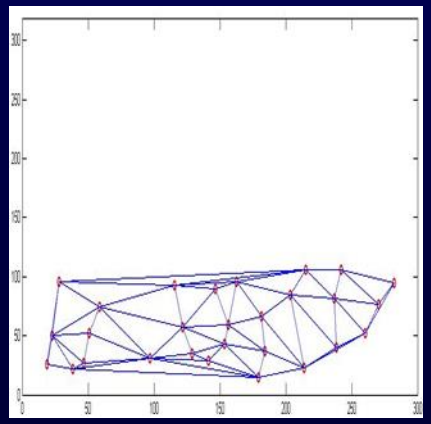
**Compute Delaunay triangles for each tissue layer**



**Top layer**



**Middle**



**Bottom**

# Experimental Results

61 cervix epithelium images, pathologist-graded

- **Mean area of triangles**
- **St. Dev. of triangle areas**
- **Mean edge length of triangles**
- **St. Dev. of edge lengths**
- **Num. of triangles in layer**
- **Num. of triangles in layer/ area of layer**
- **Other features based on nuclei**

Support Vector Machine Classifier

Normal vs. disease: 96%
Exact disease level (4 categories): 68%

# But Practical Benefit?

**In current Whole Slide Imaging systems**

**"Complete sets of WSI data are dumped into the pathologist's lap for manual interpretation. WSI systems and scanners may be automated, but not in ways that optimally support diagnostic work in an intelligent fashion."**

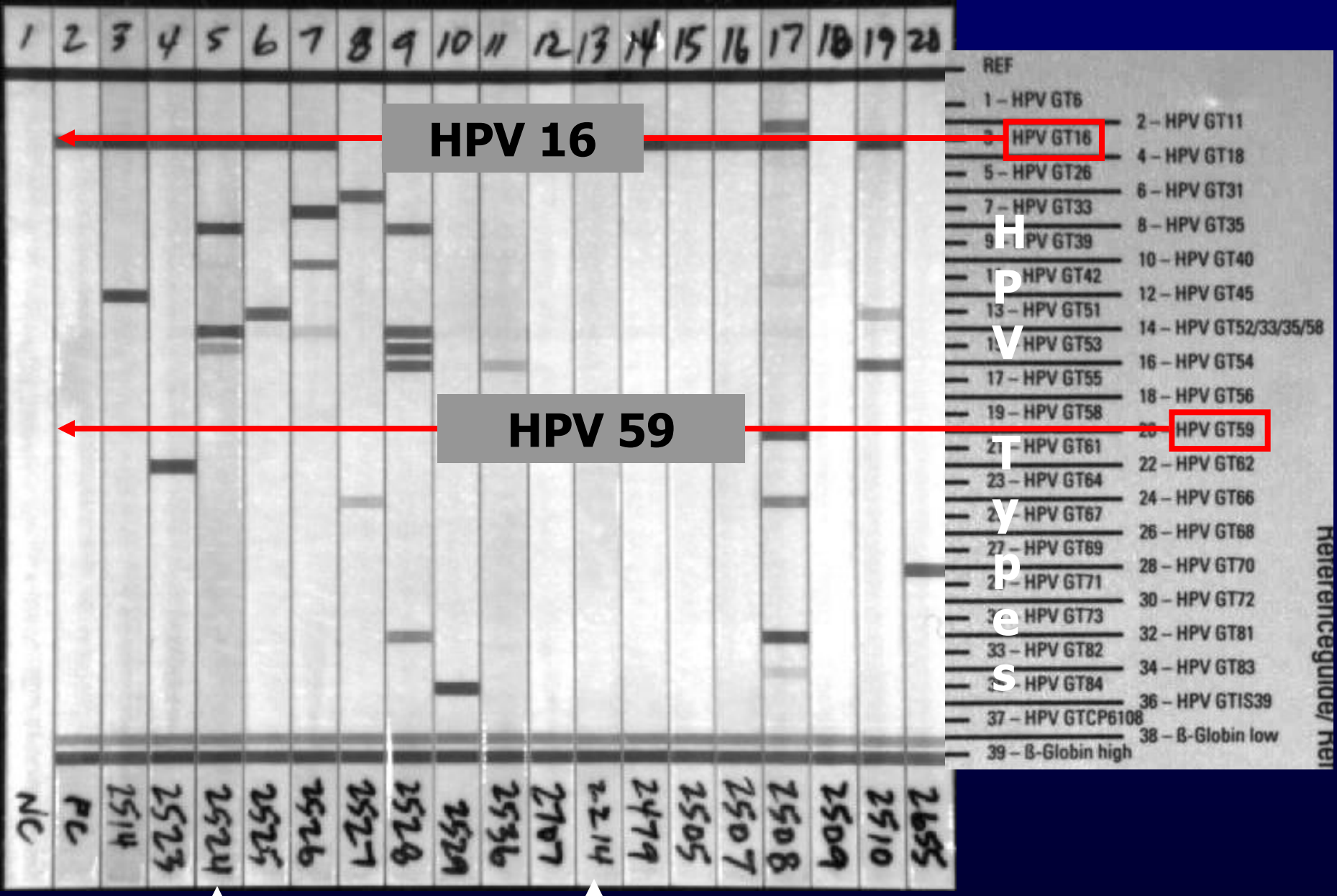
Fine, Jeffrey L. 21st century workflow: a proposal. Journal of Pathology Informatics, 28 Nov. 2014.

**"Unless something fundamentally changes the existing value proposition, WSI may not compare favorably with traditional glass workflow, given the resources and time needed to accommodate this technology."**

Fine, Jeffrey L. ibid.

# HPV Linear Array Image Processing Research

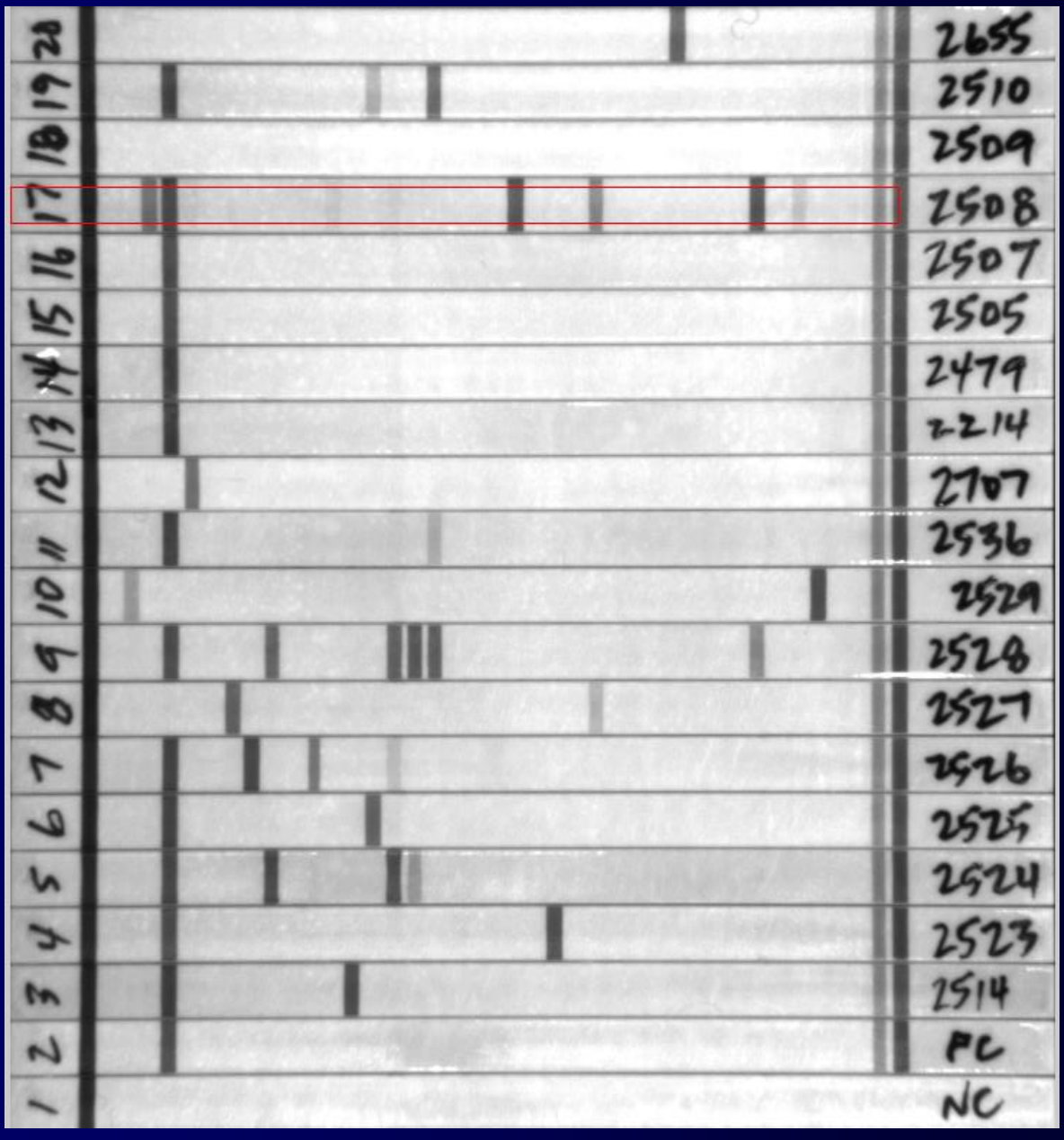
- Drs. Nico Wentzensen of NCI Clinical Genetics Branch (CGB)
- Can interpretation of HPV Linear Arrary Images be automated?
- Is machine interpretation as good as/better than human observer?




**PATIENT IDs (De-IDed)**

**Patient 2524**

**Patient 2214**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Pixel Values (0-1000 scale)

| | | | | | | |
|---|---|---|---|---|---|---|
| 514 | 517 | 520 | 539 | 528 | 530 | 530 |
| 615 | 610 | 618 | 612 | 614 | 625 | 600 |
| 651 | 649 | 651 | 652 | 657 | 653 | 644 |
| 663 | 661 | 671 | 670 | 666 | 664 | 659 |
| 678 | 680 | 676 | 673 | 667 | 682 | 674 |
| 679 | 686 | 693 | 686 | 684 | 686 | 699 |
| 704 | 698 | 702 | 698 | 686 | 703 | 715 |
| 698 | 711 | 703 | 702 | 699 | 714 | 726 |
| 724 | 699 | 699 | 707 | 707 | 724 | 725 |
| 709 | 716 | 704 | 712 | 715 | 730 | 726 |
| … | | | | | | |
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Mean pixel values

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|---|
| 525 |
| 613 |
| 651 |
| 665 |
| 676 |
| 688 |
| 701 |
| 708 |
| 712 |
| 716 |
| … |
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This is the “total signal” or “absolute signal” (“signal” + “background”).

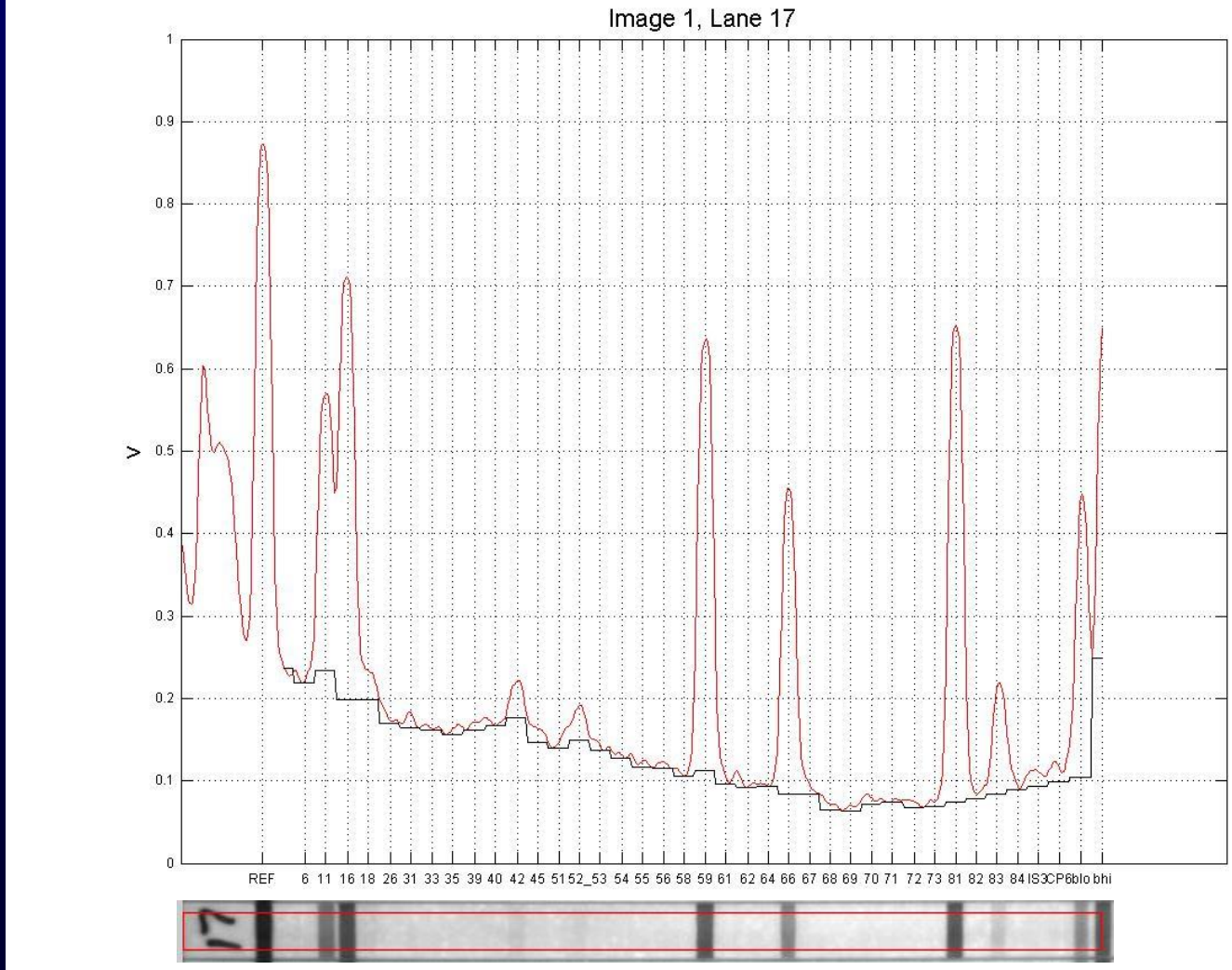
Image 1, Lane 17
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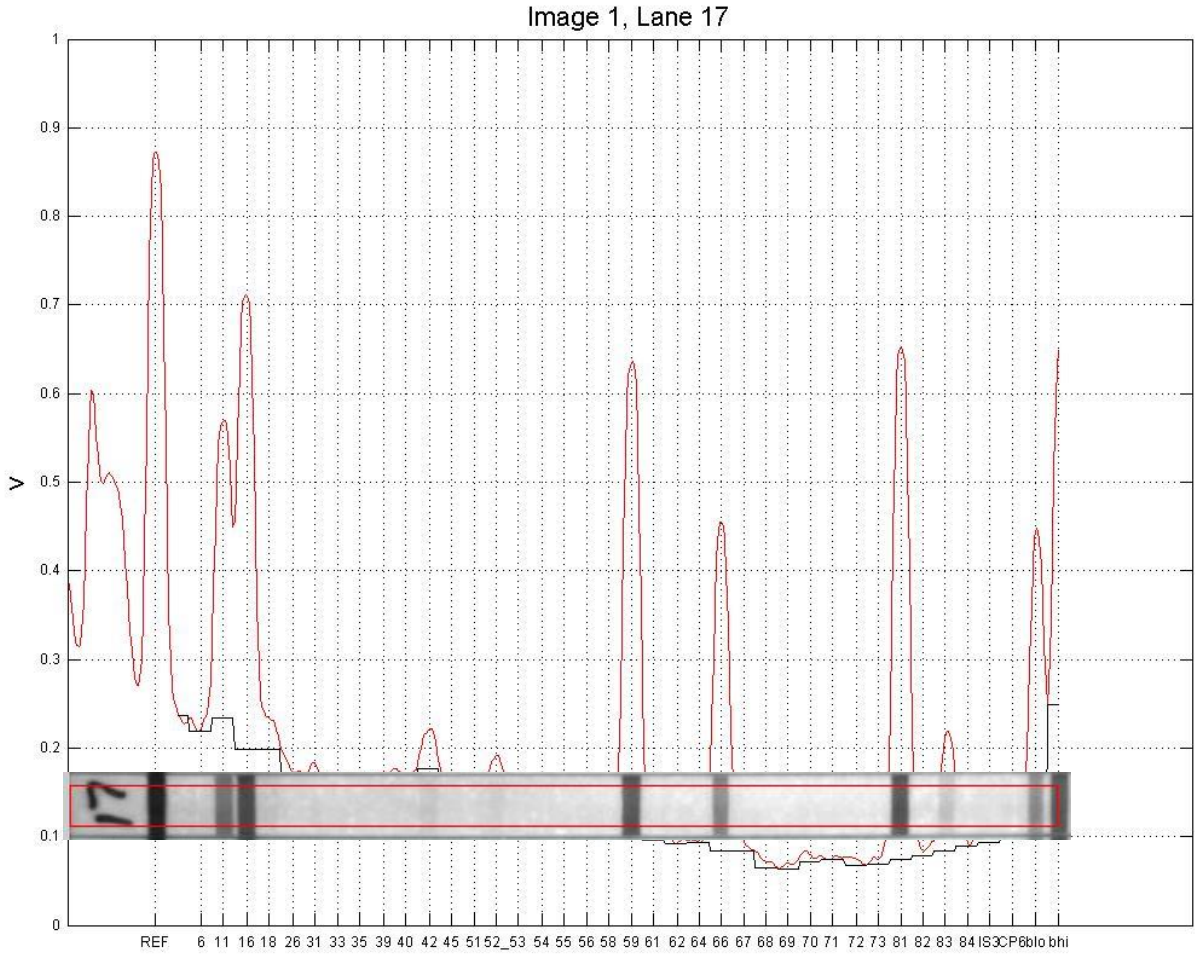
Image 1, Lane 17
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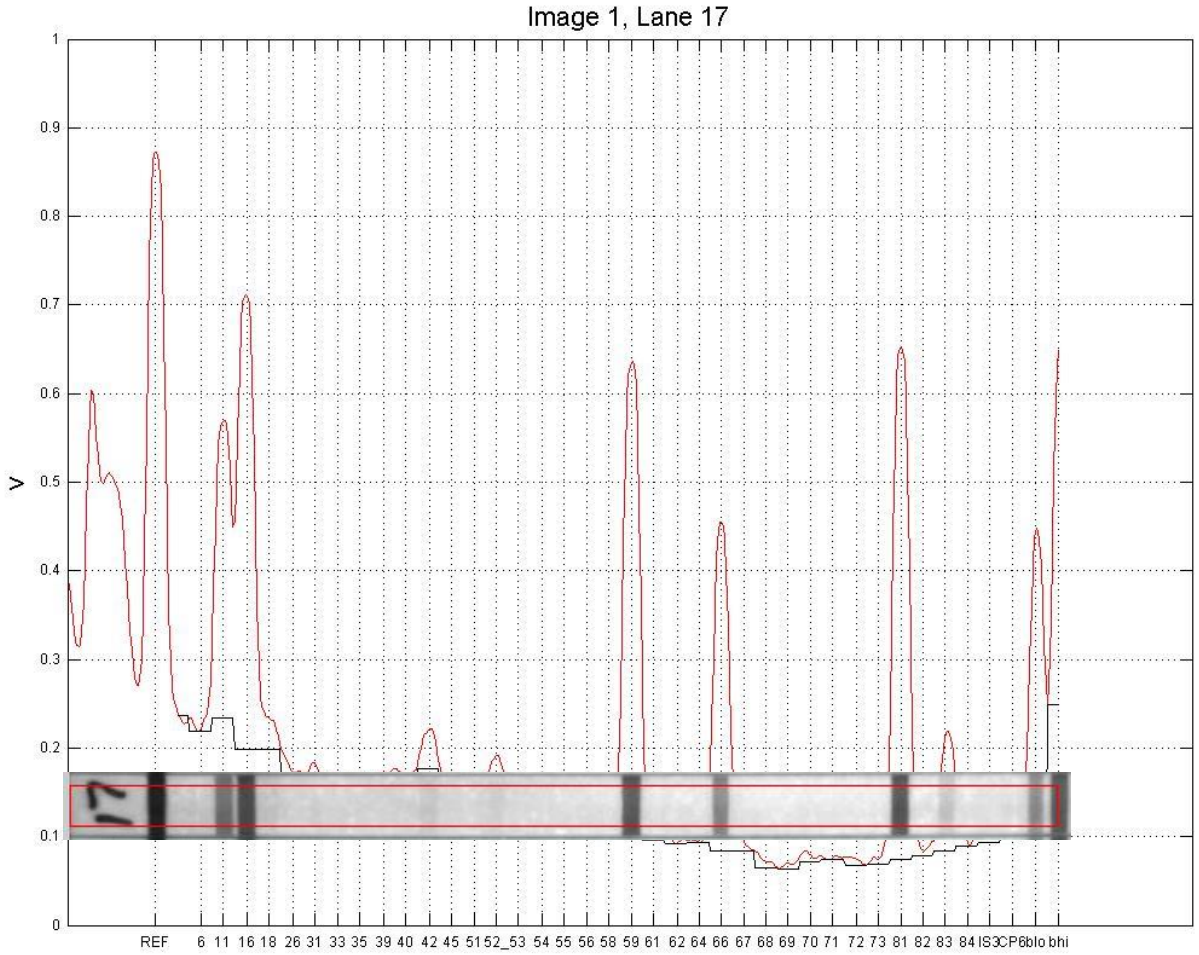
Image 1, Lane 17
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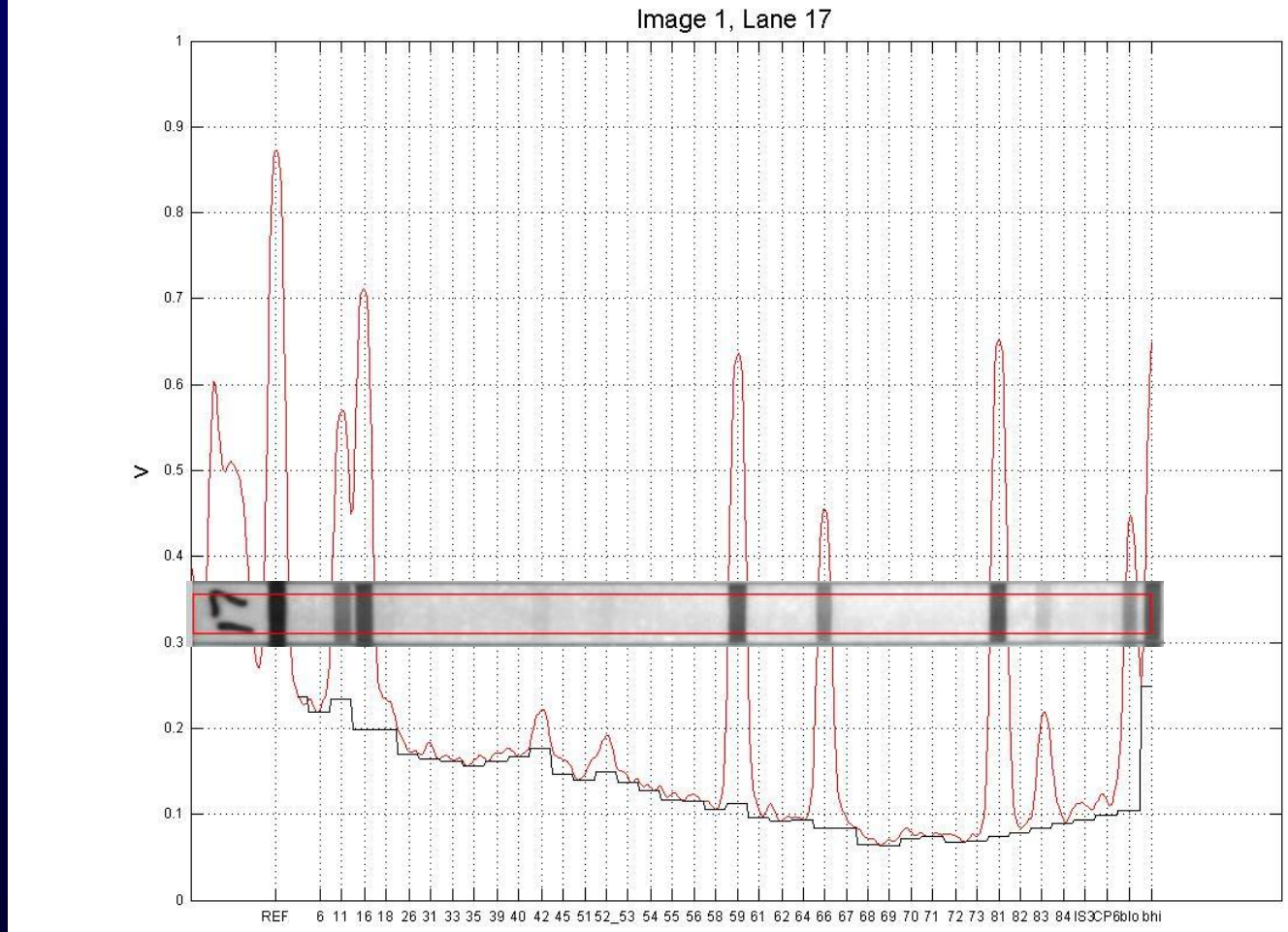
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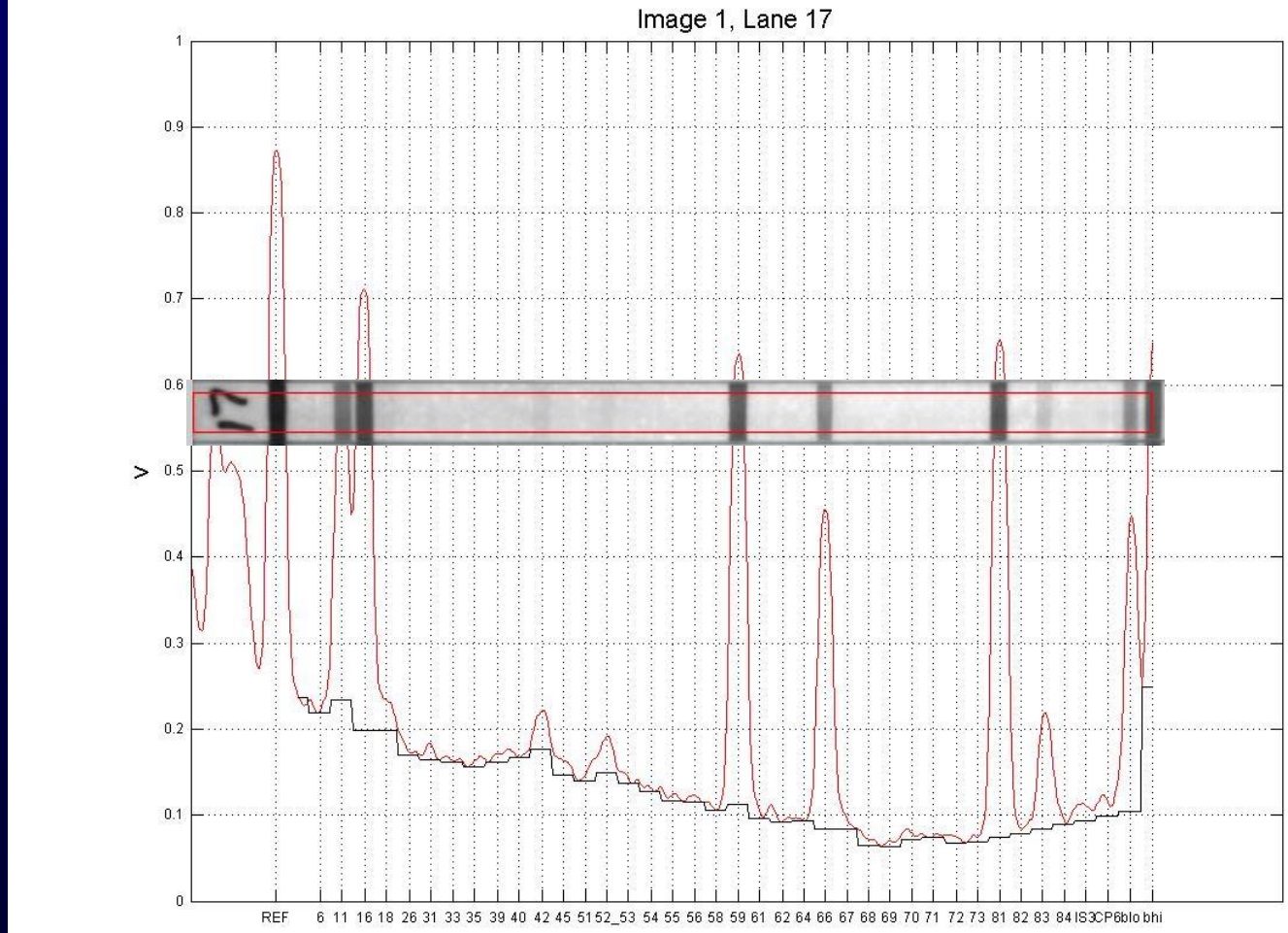
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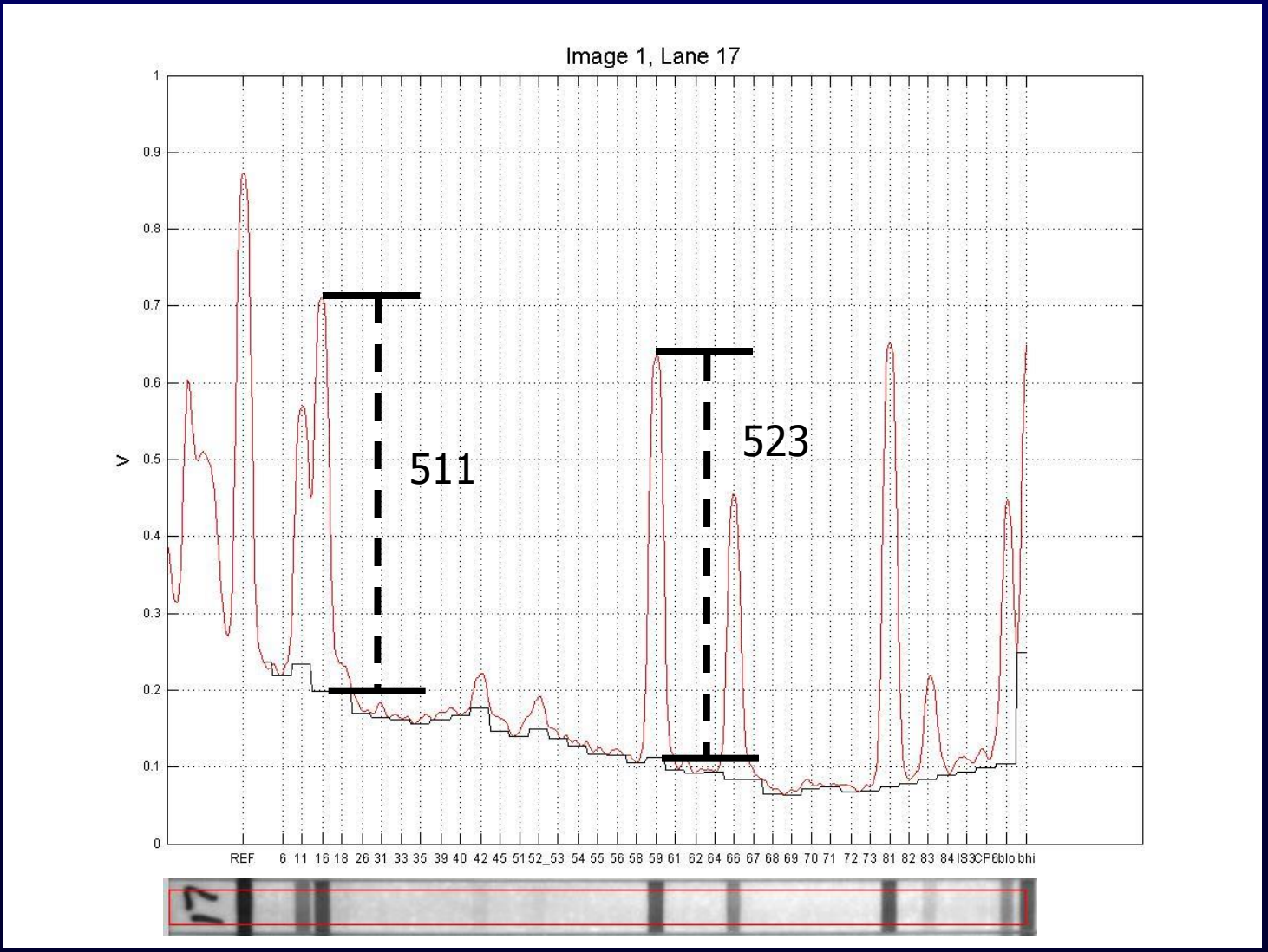
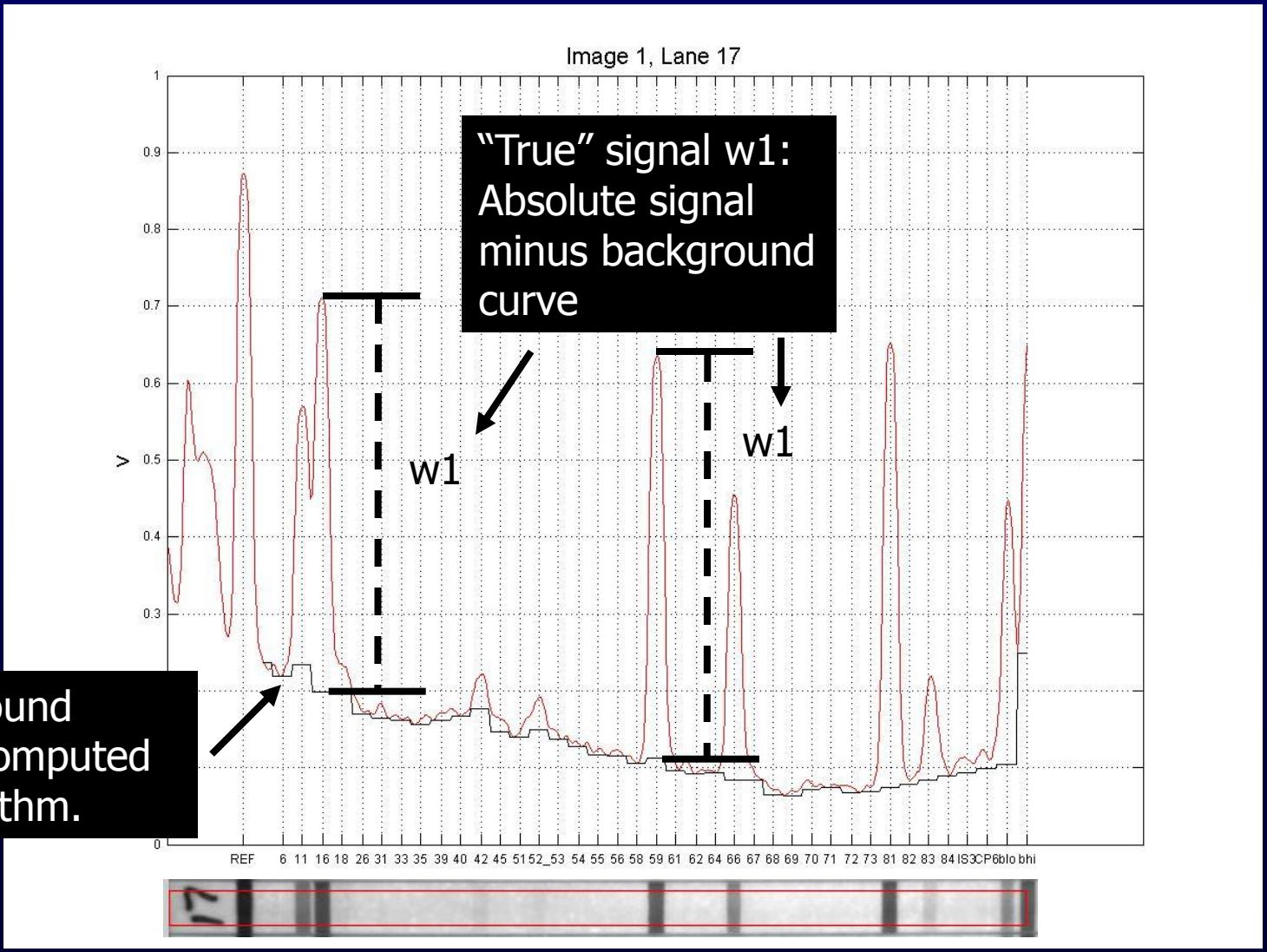
The amplitude of signal 59 is at least as strong as that of signal 16, *relative to the background*, but the absolute signal 16 is greater than absolute signal 59, because the background is not constant.



So it becomes important to separate the "true" signal—a postive response in a cell—from the "background"—the contents of the image that are not related to this response.



Microsoft Excel - w1-1-20.xls

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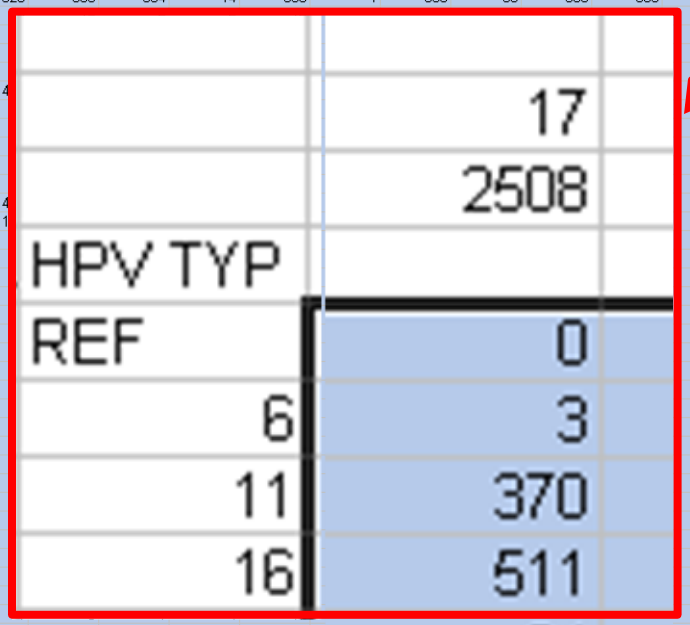
Type a question for help

Arial 10

Reply with Changes... End Review...

E9 0

| | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | | | | | LANES | | | | | | | | | | | | | | | | | | | | |
| 6 | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | |
| 7 | | | | | 0 | 1 | 2514 | 2523 | 2524 | 2525 | 2526 | 2527 | 2528 | 2529 | 2536 | 2707 | 2214 | 2479 | 2505 | 2507 | 2508 | 2509 | 2510 | 2655 | |
| 8 | | CELL | HPV CEL | HPV TYP | | | | | | | | | | | | | | | | | | | | | |
| 9 | | 1 | | REF | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 10 | | 2 | 1 | 6 | 4 | 2 | 9 | 13 | 1 | 0 | 5 | 6 | 8 | 241 | 4 | 13 | 1 | 20 | 5 | 5 | 3 | 9 | 3 | 8 | |
| 11 | | 3 | 2 | 11 | 1 | 55 | 58 | 23 | 32 | 59 | 36 | 1 | 29 | 1 | 37 | 13 | 44 | 59 | 27 | 33 | 370 | 7 | 20 | 15 | |
| 12 | | 4 | 3 | 16 | 0 | 565 | 541 | 493 | 520 | 565 | 534 | 14 | 530 | 1 | 558 | 38 | 586 | 605 | 559 | 569 | 511 | 7 | 550 | 12 | |
| 13 | | 5 | 4 | 18 | 4 | 19 | 14 | 3 | | | | | | | | | | | 6 | 21 | 34 | 0 | 11 | 12 | |
| 14 | | 6 | 5 | 26 | 11 | 6 | 4 | 4 | | | | | | | | | | | 12 | 9 | 3 | 11 | 12 | 5 | |
| 15 | | 7 | 6 | 31 | 1 | 4 | 8 | 2 | | | | | | | | | | | | 7 | 18 | 3 | 10 | 5 | |
| 16 | | 8 | 7 | 33 | 1 | 1 | | 3 | | | | | | | | | | | 3 | 21 | 2 | 4 | 0 | 4 | |
| 17 | | 9 | 8 | 35 | 30 | 21 | 3 | 22 | 4 | | | | | | | | | | 2 | 6 | 7 | 12 | 4 | 10 | |
| 18 | | 10 | 9 | 39 | 3 | 12 | 7 | | | | | | | | | | | | 3 | 0 | 10 | 11 | 2 | 0 | |
| 19 | | 11 | 10 | 40 | 29 | 7 | 2 | 9 | | | | | | | | | | | 17 | 9 | 0 | 33 | 7 | 18 | |
| 20 | | 12 | 11 | 42 | 12 | 1 | 6 | 7 | | | | | | | | | | | 12 | 2 | 45 | 10 | 1 | 6 | |
| 21 | | 13 | 12 | 45 | 4 | 3 | 513 | 1 | | | | | | | | | | | 9 | 7 | 16 | 6 | 18 | 6 | |
| 22 | | 14 | 13 | 51 | 7 | 10 | 0 | 11 | | | | | | | | | | | 1 | 13 | 7 | 0 | 227 | 2 | |
| 23 | | 15 | 14 | 52_ | 1 | 36 | 13 | 13 | 4 | | | | | | | | | | 26 | 32 | 42 | 4 | 33 | 10 | |
| 24 | | 16 | 15 | 53 | 1 | 83 | 0 | 12 | 1 | | | | | | | | | | 1 | 2 | 4 | 2 | 6 | 4 | |
| 25 | | 17 | 16 | 54 | 8 | 64 | 1 | 2 | | | | | | | | | | | 6 | 7 | 4 | 8 | 507 | 3 | |
| 26 | | 18 | 17 | 55 | 21 | 65 | 0 | 18 | | | | | | | | | | | 15 | 19 | 8 | 4 | 5 | 7 | |
| 27 | | 19 | 18 | 56 | 19 | 42 | 0 | 3 | | | | | | | | | | | 14 | 23 | 9 | 6 | 1 | 1 | |
| 28 | | 20 | 19 | 58 | 6 | 2 | 3 | 12 | | | | | | | | | | | 1 | 15 | 0 | 2 | 1 | 0 | |
| 29 | | 21 | 20 | 59 | 30 | 21 | 12 | 6 | | | | | | | | | | | 2 | 23 | 523 | 6 | 3 | 0 | |
| 30 | | 22 | 21 | 61 | 10 | 9 | 1 | 31 | | | | | | | | | | | 2 | 12 | 9 | 0 | 8 | 6 | |
| 31 | | 23 | 22 | 62 | 18 | 0 | 7 | 557 | | | | | | | | | | | 8 | 6 | 0 | 1 | 5 | 2 | |
| 32 | | 24 | 23 | 64 | 6 | 3 | 7 | 2 | | | | | | | | | | | 9 | 4 | 9 | 2 | 11 | 5 | |
| 33 | | 25 | 24 | 66 | 15 | 10 | 10 | 7 | | | | | | | | | | | 7 | 1 | 371 | 6 | 3 | 3 | |
| 34 | | 26 | 25 | 67 | 11 | 9 | 3 | 2 | | | | | | | | | | | 4 | 22 | 11 | 4 | 1 | 4 | |
| 35 | | 27 | 26 | 68 | 2 | 3 | 7 | 4 | | | | | | | | | | | 9 | 17 | 6 | 0 | 3 | 2 | |
| 36 | | 28 | 27 | 69 | 3 | 0 | 0 | 0 | | | | | | | | | | | 11 | 14 | 6 | 0 | 9 | 2 | |
| 37 | | 29 | 28 | 70 | 1 | 14 | 2 | 5 | | | | | | | | | | | 10 | 1 | 9 | 1 | 6 | 552 | |
| 38 | | 30 | 29 | 71 | 0 | 2 | 10 | 6 | | | | | | | | | | | 10 | 3 | 2 | 1 | 4 | 7 | |
| 39 | | 31 | 30 | 72 | 3 | 11 | 4 | 1 | | | | | | | | | | | 5 | 1 | 7 | 3 | 1 | 3 | |
| 40 | | 32 | 31 | 73 | 13 | 4 | 1 | 3 | | | | | | | | | | | 17 | 18 | 6 | 4 | 10 | 11 | |
| 41 | | 33 | 32 | 81 | 3 | 20 | 0 | 20 | | | | | | | | | | | 5 | 3 | 574 | 0 | 11 | 2 | |
| 42 | | 34 | 33 | 82 | 0 | 18 | 2 | 3 | | | | | | | | | | | 6 | 2 | 0 | 1 | 7 | 4 | |
| 43 | | 35 | 34 | 83 | 17 | 10 | 10 | 2 | | | | | | | | | | | 26 | 24 | 117 | 0 | 14 | 6 | |
| 44 | | 36 | 35 | 84 | 17 | 7 | 2 | 8 | | | | | | | | | | | 19 | 50 | 3 | 11 | 16 | 11 | |
| 45 | | 37 | 36 | IS3 | 9 | 7 | 10 | 4 | | | | | | | | | | | 39 | 68 | 6 | 12 | 16 | 12 | |
| 46 | | 38 | 37 | CP6 | 16 | 8 | 12 | 6 | 1 | 8 | 2 | 1 | 33 | 49 | 27 | 14 | 20 | 61 | 40 | 67 | 7 | 19 | 17 | 12 | |
| 47 | | 39 | | blo | 7 | 356 | 285 | 342 | 326 | 340 | 329 | 345 | 326 | 321 | 289 | 363 | 325 | 366 | 386 | 355 | 303 | 363 | 341 | 307 | |
| 48 | | 40 | | bhi | 1 | 433 | 387 | 430 | 424 | 431 | 434 | 425 | 403 | 442 | 402 | 403 | 392 | 431 | 419 | 423 | 400 | 434 | 383 | 360 | |
| 49 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 50 | | | | | | | | | | | | | | | | | | | | | | | | | |




Sheet1 Sheet2 Sheet3 Sheet4 Sheet5 Sheet6 Sheet7 Sheet8 Sheet9 Sheet10 Sheet11 Sheet12 Sheet13

Ready

Sum=40899

JOURNAL OF CLINICAL MICROBIOLOGY, Aug. 2008, p. 2759–2765 Vol. 46, No. 8
0095-1137/08/$08.00+0 doi:10.1128/JCM.00188-08


# Evaluation of Linear Array Human Papillomavirus Genotyping Using Automatic Optical Imaging Software[▽]

J. Jeronimo,[1]* N. Wentzensen,[1] R. Long,[2] M. Schiffman,[1] S. T. Dunn,[3] R. A. Allen,[3] J. L. Walker,[4] M. A. Gold,[4] R. E. Zuna,[3] M. E. Sherman,[1] S. Wacholder,[1] and S. S. Wang[1]

*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland[1]; Communications Engineering Branch, National Library of Medicine, Bethesda, Maryland[2]; Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Olahoma[3]; and Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma[4]*

Received 29 January 2008/Returned for modification 24 March 2008/Accepted 2 June 2008

**…but too many strips (~30% or more) where background removal not reliable; method has not evolved to practical level**

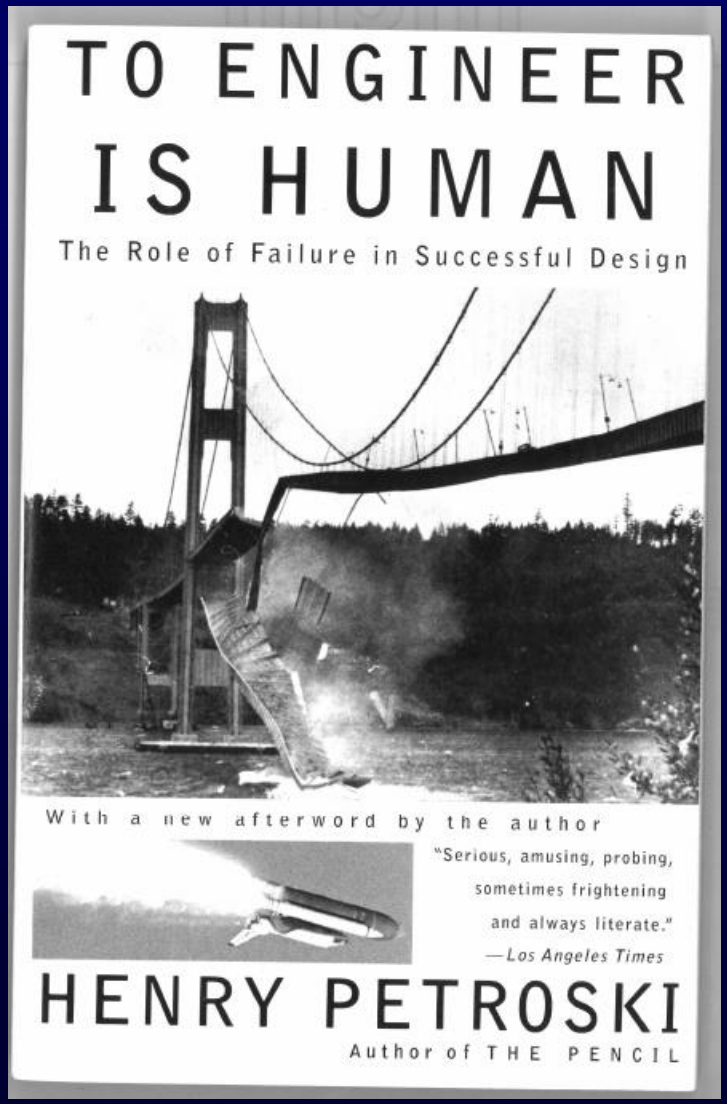
- Complex algorithms are not always essential to have significant impact.
- User value goes up as dependency on computer specialists goes down.
- Engineers need the basic vocabulary and concepts of their medical application domain; medical experts need to be able to interpret quantitative system output.
- Small systems have a natural fit for problem- solving in low-resource areas.
- Advanced algorithms may provide critical assistance to the clinician, but workflow can be a showstopper.
- **Attention to error and failure modes may yield the biggest payoff in building practical systems.**

# Anticipating System Error and Failure

**"Failure is central to engineering. Every single calculation that an engineer makes is a failure calculation.**

**Successful engineering is all about understanding how things break or fail."**

Henry Petroski

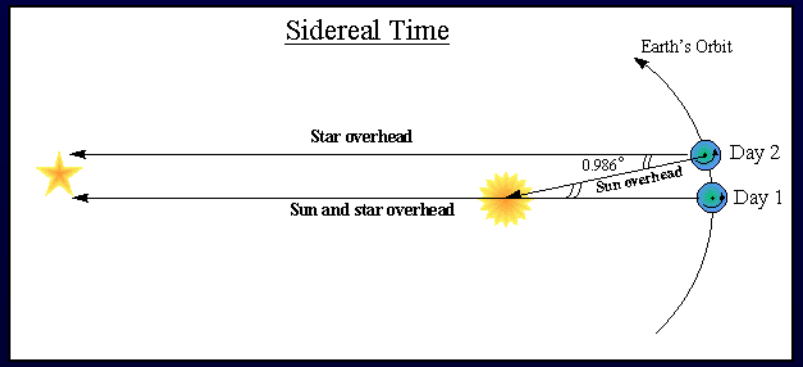


# Gemini 5

## August 21-29, 1965

Could a programmer with better domain knowledge prevented this?

- Astronauts missed their planned landing point by 91 nautical miles.
- Problem traced to programming error
- The earth rotates 360.98° degrees each solar day.
- Program code omitted the 0.98° .
- Range vector error of 7.9° accumulated over the 8-day flight.

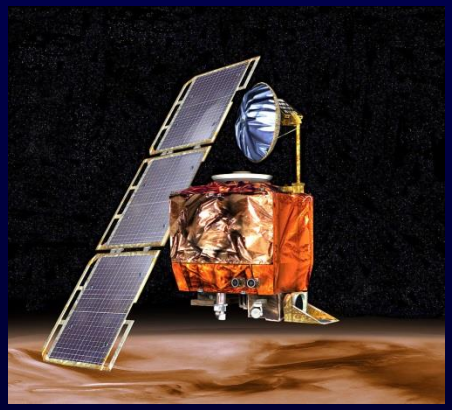



Shayler, David. Gemini: steps to the moon

# Other Notable System Errors Attributable to Software

**USS Yorktown – Sept. 21, 1997**

- All propulsion systems stopped.
- 3 hours to attach emergency engine controls.
- 2 days to fix software, repair the engines.
- Problem traced to divide-by-zero.
- Example of emergent system property?



**Mars Climate Orbiter – Sept. 23, 1999**

- Lost and presumed destroyed as it was inserted into orbit around Mars.
- Ground software commanded the spacecraft controls in British units…
- …but the spacecraft was designed to expect metric units.

# Fruitful Areas for Our Own Error/Failure Analyses?

Essay

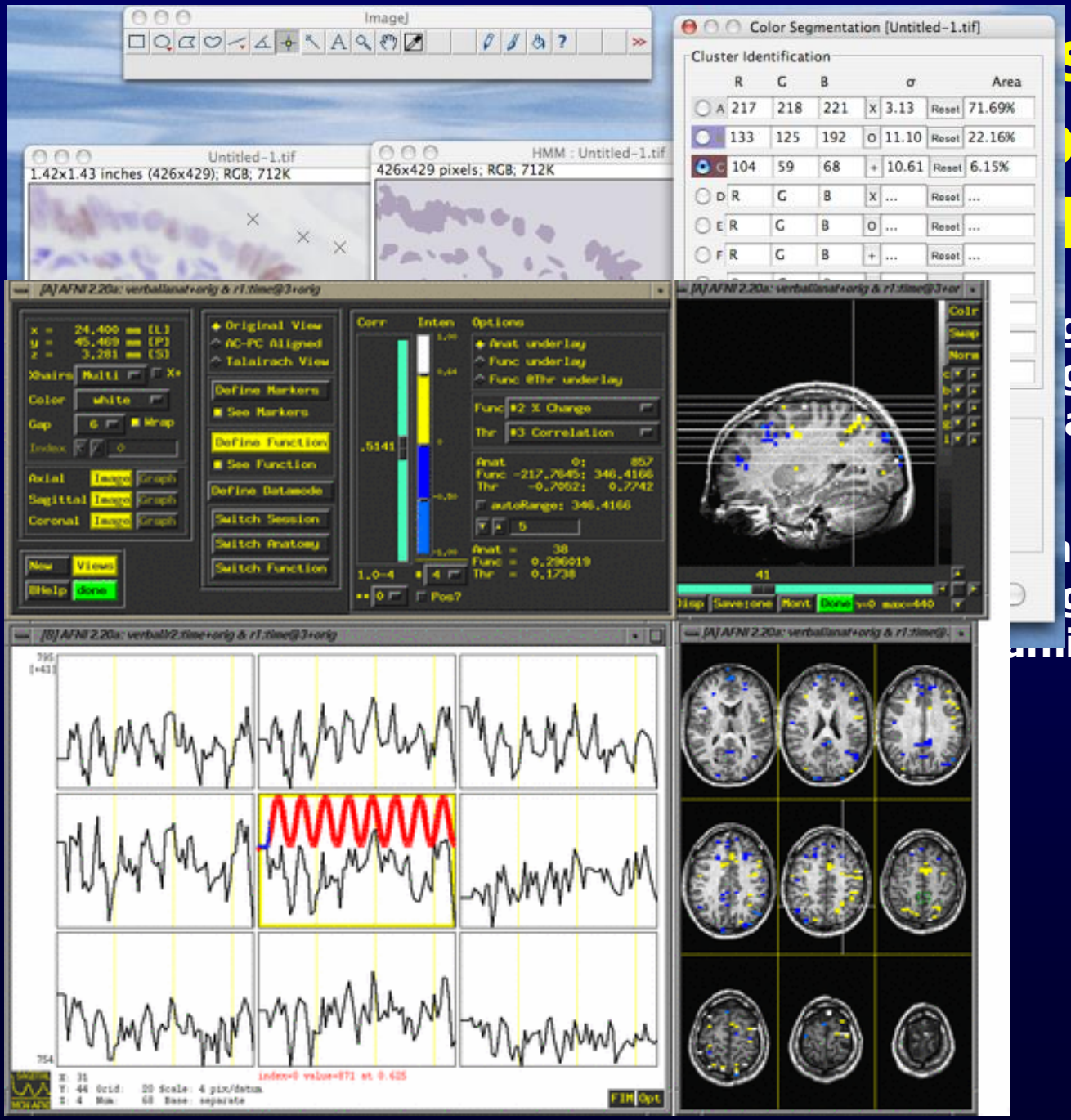
## Why Most Published Research Findings

# NIH plans to enhance reproducibility

**Francis S. Collins** and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

PLOS, 2005

Nature, 30 Jan 2014




# ssful ons from Institutes

general image g agej.nih.gov

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# Inviting Areas for Future Practical Research

nih record

**President, Collins Announce BRAIN Initiative**

On Apr. 2, in the East Room of the White House, President Obama announced the administration's BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. The President was introduced by NIH director Dr. Francis Collins, who in the days following the announcement embarked on a media outreach tour to sketch out the particulars of a plan he called roughly reminiscent of the Hu-

nih record

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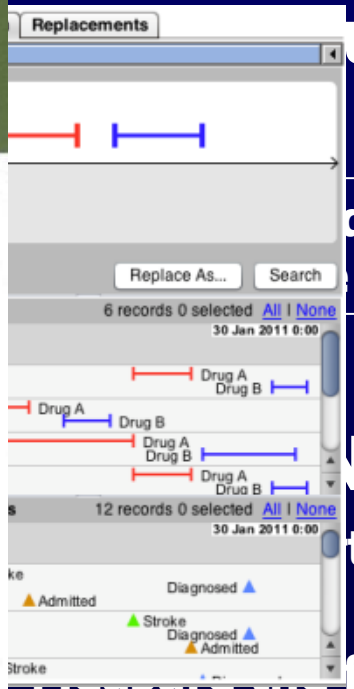
NIH would lead an effort, slated to begin in FY 2014, budgeted in its first year at $100 million. In concert with research teams from the Defense Advanced Research Projects Agency and the National Science Foundation, NIH would spearhead an initiative to accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain

SEE BRAIN INITIATIVE, PAGE 6

*President Barack Obama (r) is introduced by NIH director Dr. Francis Collins at the BRAIN Initiative event at the White House on Apr. 2.*

PHOTO: CHUCK KENNEDY




uery

d
Lab

N Initiative

t to map circuitry

fluctuating patterns of electrical/chemical activity

Understand how their interplay creates our cognitive/behavioral capabilities

# Is the Future Big and Deep?

## ImageNet Classification with Deep Convolutional Neural Networks

**Alex Krizhevsky**
University of Toronto
kriz@cs.utoronto.ca

**Ilya Sutskever**
University of Toronto
ilya@cs.utoronto.ca

**Geoffrey E. Hinton**
University of Toronto
hinton@cs.utoronto.ca

- 8-layer deep convolutional neural network: 5 convolutional layers, 3 fully connected. Trained on 1.2 million labeled images; 1000 different categories.
- Six days of training on two-GPU system.
- Tested classification of 150,000 images into 1000 categories.
- Top-5 error rate 15.3%.
- More than 10% points better than second-place in ILSVC-2012 competition.

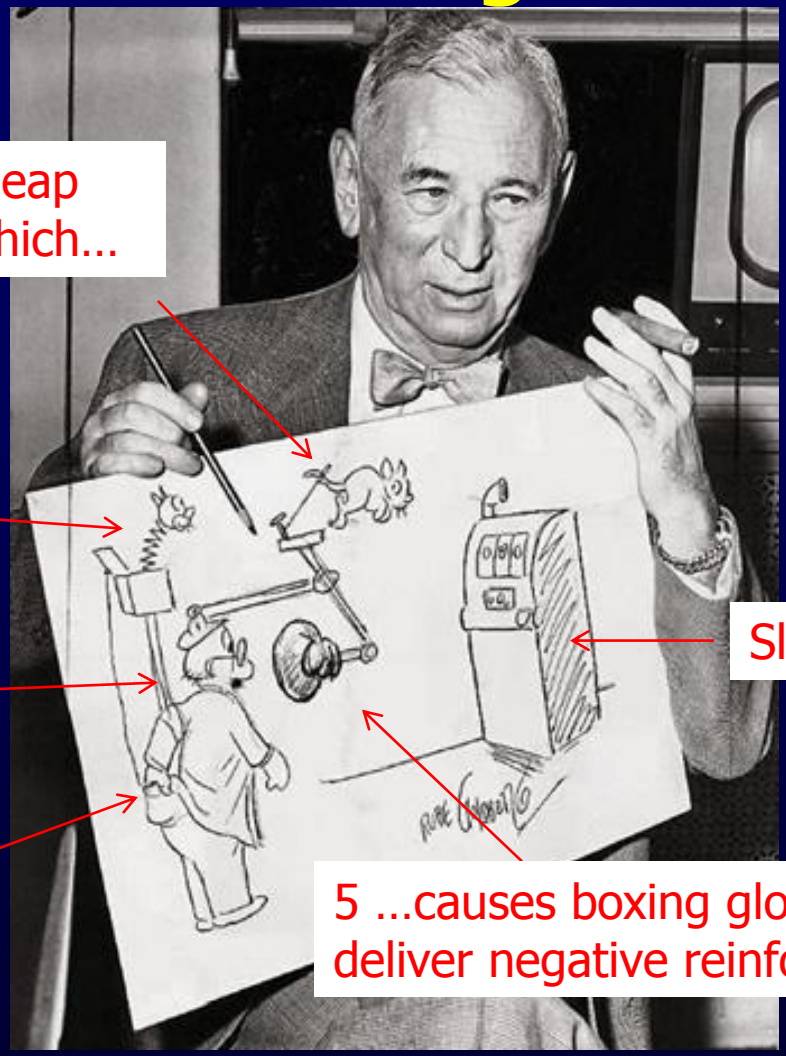
# Closing Thought….

**"Although engineers want always to make everything better, they cannot make anything perfect.**

**This basic characteristic flaw of the products of the profession's practitioners is what drives change and makes achievement a process rather than a goal. "**

-- Henry Petroski

# Closing System…
# System to Break Gambling Habit



4 …frightens animal to leap from counter-weight, which…

3 …activates Jack-in-the-Box, which…

2 …arm motion…

1 Man sees slot machine, reaches for wallet…

Slot machine

5 …causes boxing glove to deliver negative reinforcement…

R. Goldberg

# THANK YOU

Gynecologic Oncology 135 (2014) 201–207

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# The increased detection of cervical intraepithelial neoplasia when using a second biopsy at colposcopy

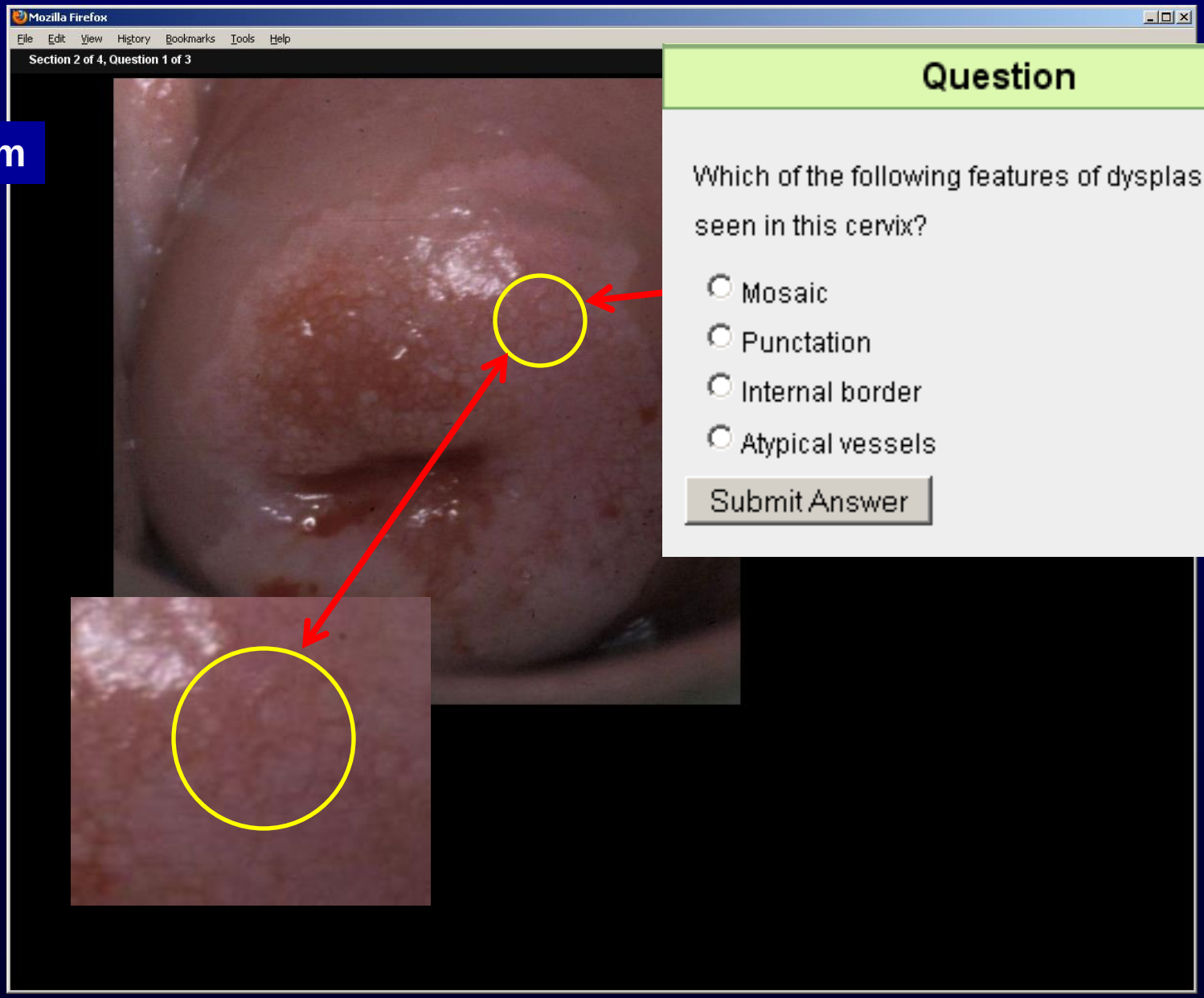
- Similar study was carried out (using the Boundary Marking Tool) for 610 women in Spain and the Netherlands.

- Detection of moderate/high-grade lesions (CIN2+) increased from 83% (one biopsy) to 93% (two biopsies).

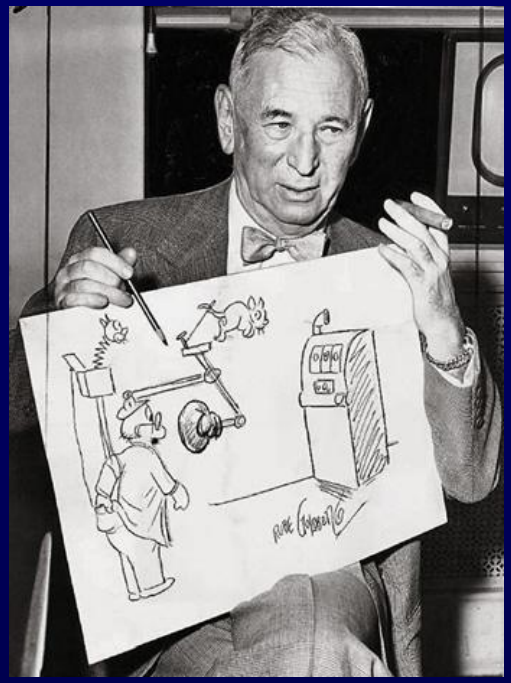
*Conclusions.* A second lesion-directed biopsy is associated with a significant increase in CIN2 + detection. Performing a second lesion-directed biopsy and using a low threshold for abnormality of any acetowhitening should become the standard clinical practice of colposcopy.

van der Marel, et al, Sep. 2014

# Mosaicism


Mozilla Firefox
File Edit View History Bookmarks Tools Help
Section 2 of 4, Question 1 of 3
Question
Which of the following features of dysplasia is seen in this cervix?
Mosaic
Punctation
Internal border
Atypical vessels
Submit Answer

| Pool | | Num Ques Avail | Choose This Num | Cumulative Num |
|---|---|---|---|---|
| 1 | Case, Normal | 9x3 | 2x3 | 6 |
| 2 | Case, LSIL | 15x3 | 4x3 | 18 |
| 3 | Case, HSIL | 49x3 | 6x3 | 36 |
| 4 | Slide ID, V/V | 4 | 3 | 39 |
| 5 | Slide ID,Colpo,Ca | 8 | 2 | 41 |
| 6 | Slide ID,Colpo,Nrml | 10 | 2 | 43 |
| 7 | Slide ID, LSIL | 18 | 1 | 44 |
| 8 | Slide ID, HSIL | 44 | 2 | 46 |
| 9 | Slide ID, Dysplasia | 14 | 3 | 49 |
| 10 | Mult Ch,Med Knldge | 30 | 12 | 61 |
| 11 | Mult Ch,Mgt, HSIL | 11 | 4 | 65 |
| 12 | Mult Ch,Mgt, Adoles | 7 | 2 | 67 |
| 13 | Mult Ch,Mgt, Gland | 7 | 2 | 69 |
| 14 | Mult Ch,Mgt,AS/LSIL | 15 | 4 | 73 |
| 15 | Mult Ch,Mgt,CIN1 | 9 | 1 | 74 |



- Reuben Lucius Goldberg (1883-1970) popularized these systems
- They came to be called “Rube Goldberg machines”

They symbolize, he said,

**“Man’s capacity for exerting maximum effort to achieve minimum results”**

# IDEA

**Quantitative question analysis may help us identify questions**

- **which are poorly constructed, or**

- **where we should focus on better Resident training.**

**This may be high-value capability to incorporate into the system.**

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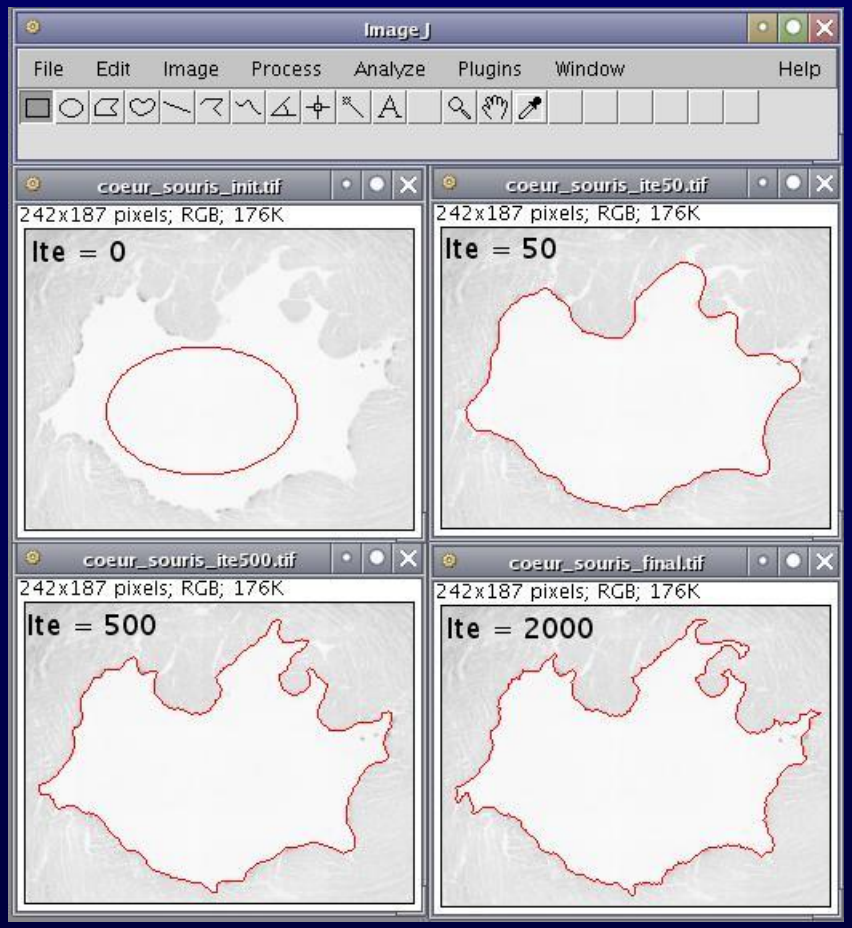
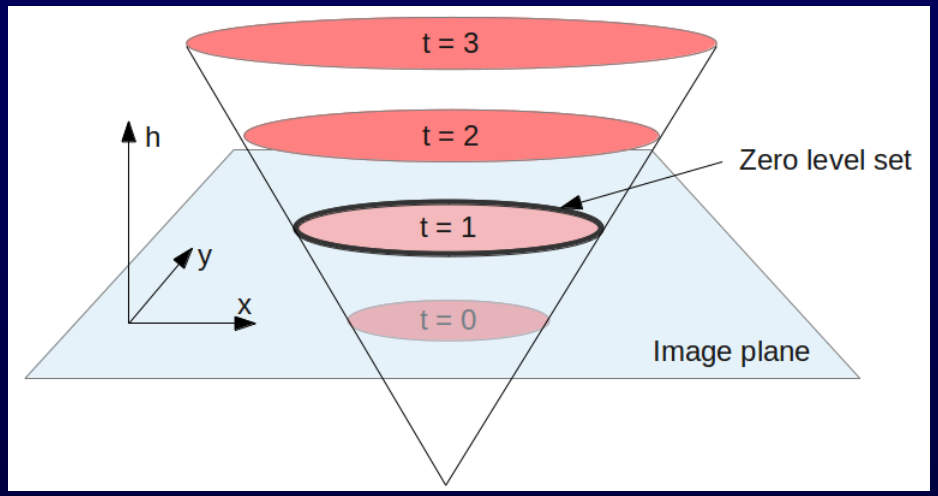

ImageJ
File Edit Image Process Analyze Plugins Window Help
coeur_souris_init.tif
242x187 pixels; RGB; 176K
Ite = 0
coeur_souris_ite50.tif
242x187 pixels; RGB; 176K
Ite = 50
coeur_souris_ite500.tif
242x187 pixels; RGB; 176K
Ite = 500
coeur_souris_final.tif
242x187 pixels; RGB; 176K
Ite = 2000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Zero level set
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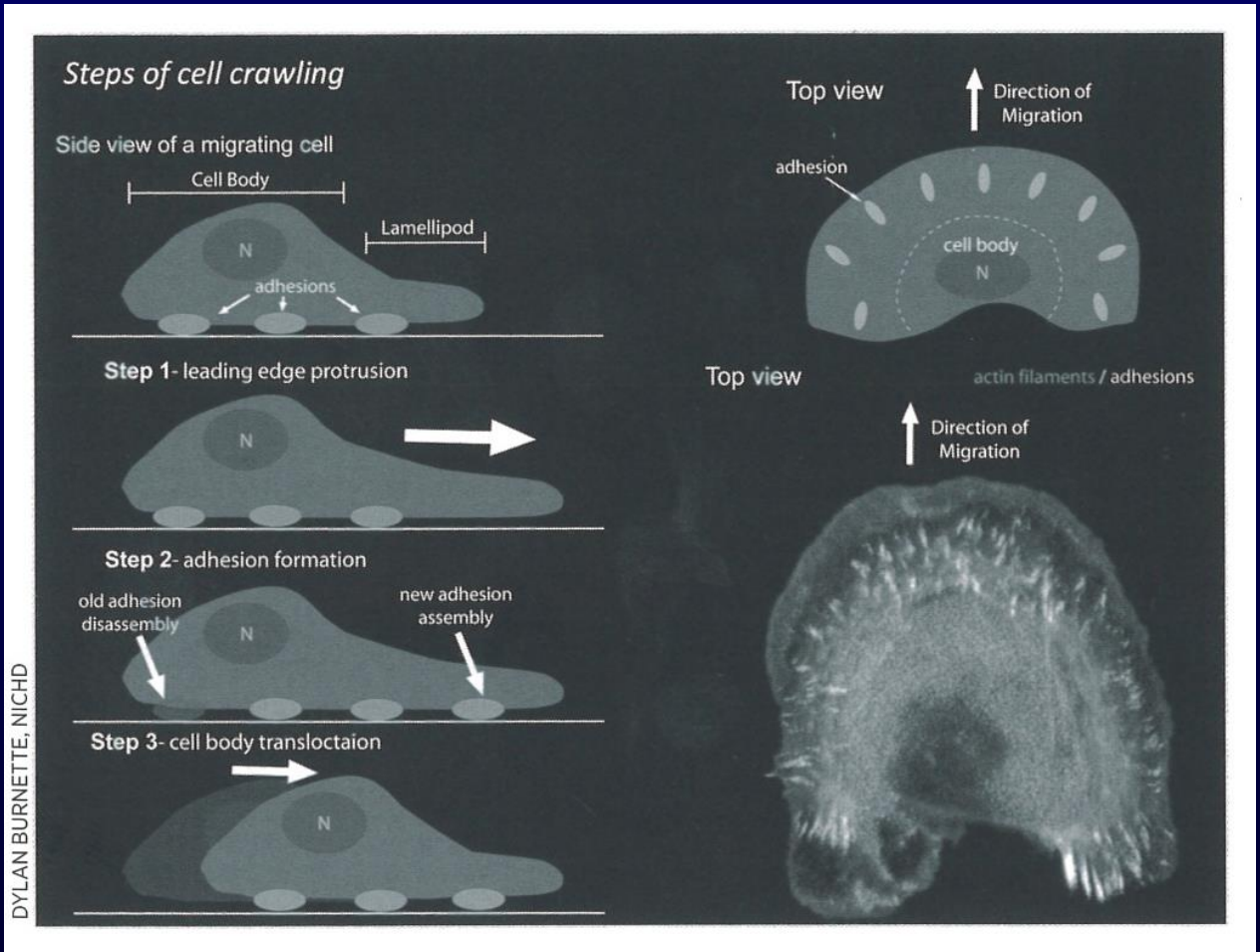



The NIH Catalyst, 21(5), Sep-Oct 2013, p. 6.

nih record

## President, Collins Announce BRAIN Initiative

On Apr. 2, in the East Room of the White House, President Obama announced the administration's BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. The President was introduced by NIH director Dr. Francis Collins, who in the days following the announcement embarked on a media outreach tour to sketch out the particulars of a plan he called roughly reminiscent of the Human Genome Project, circa 1988.

NIH would lead an effort, slated to begin in FY 2014, budgeted in its first year at $100 million. In concert with research teams from the Defense Advanced Research Projects Agency and the National Science Foundation, NIH would spearhead an initiative to accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain

SEE **BRAIN INITIATIVE,** PAGE 6


*President Barack Obama (r) is introduced by NIH director Dr. Francis Collins at the BRAIN Initiative event at the White House on Apr. 2.*

PHOTO: CHUCK KENNEDY

NIH Record, LXV(9), April 26, 2013, p.1.

FRANK DELEO, NIAID

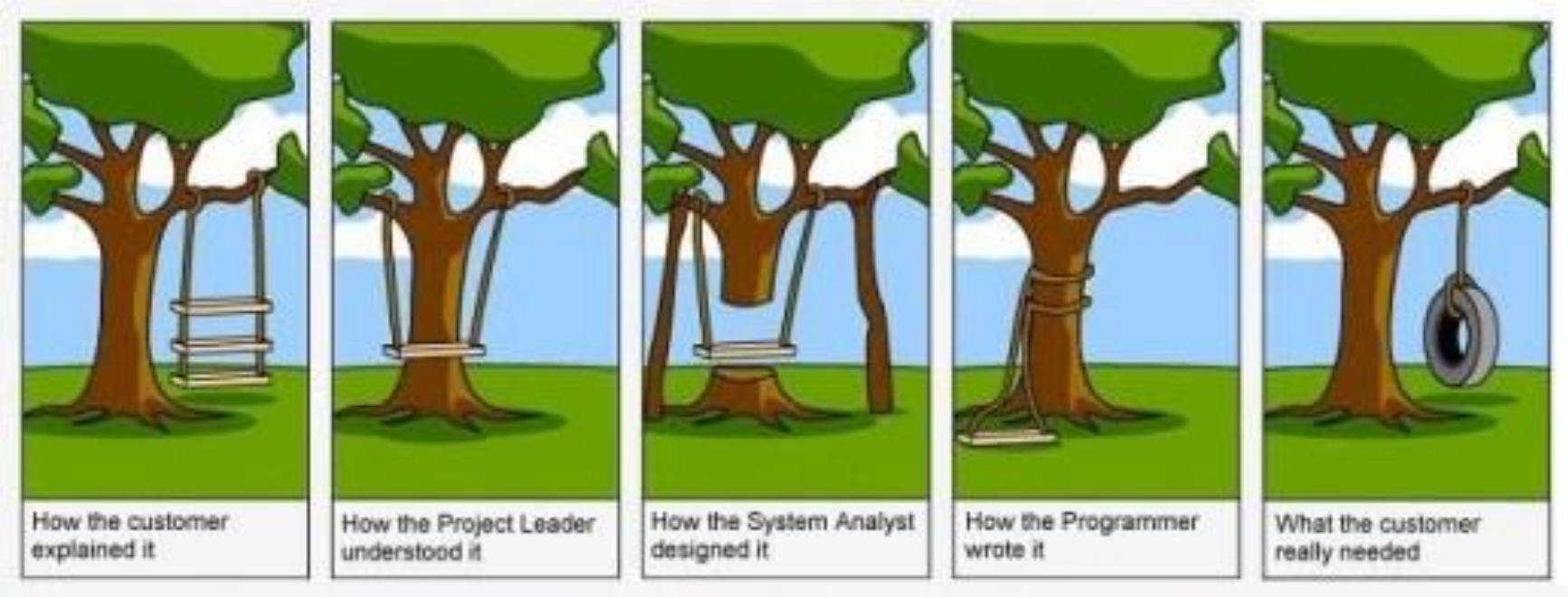
Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria (ball-like structures) are bursting out of a dead neutrophil.

The NIH Catalyst, 20(6),Nov-Dec 2012, p.1.

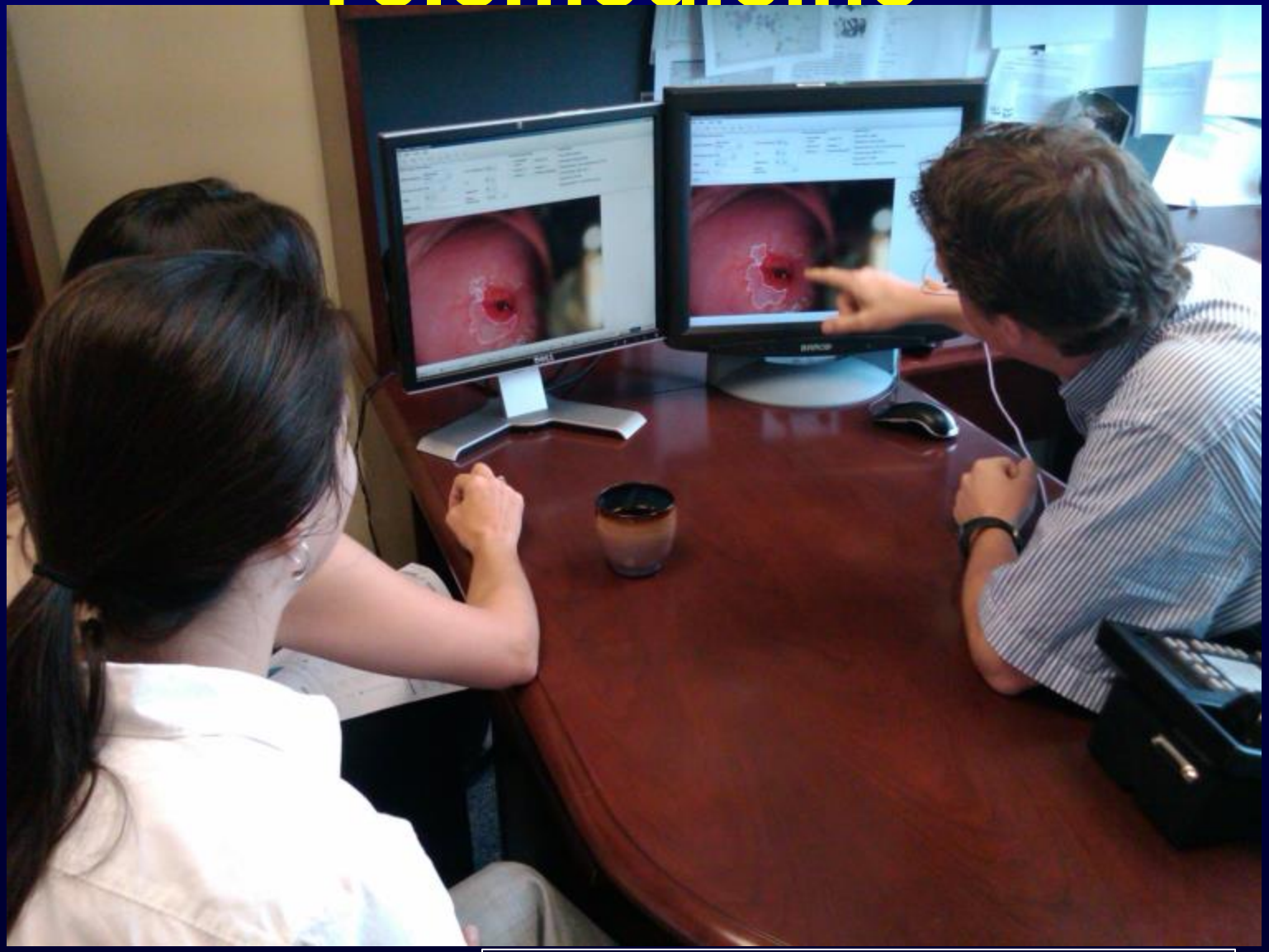
- Sometimes simple human interaction beats sophisticated algorithms.
- User value goes up as dependency on computer specialists goes down.
- Engineers need the vocabulary and basic concepts of the medical domain for which they are designing systems; medical experts need an understanding of quantitative methods required to interpret the system output.
- You get the best answers (especially from medical experts) when you don't as muddled questions.
- Corollary: If you to minimize variability in classification of images by medical experts, give the experts good image examples of the classes.

Poyla, etc.

# Practicality of Development…



# Case conference – “Telemedicine”

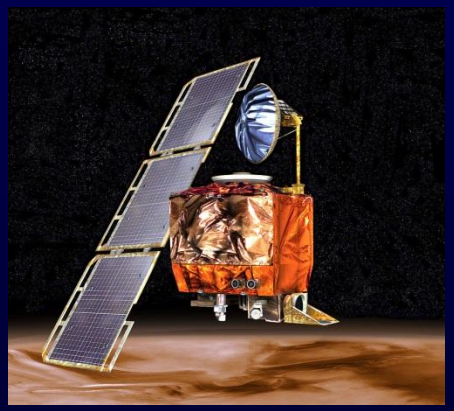


Slide used by permission of Dr. Nicholas Wentzensen,

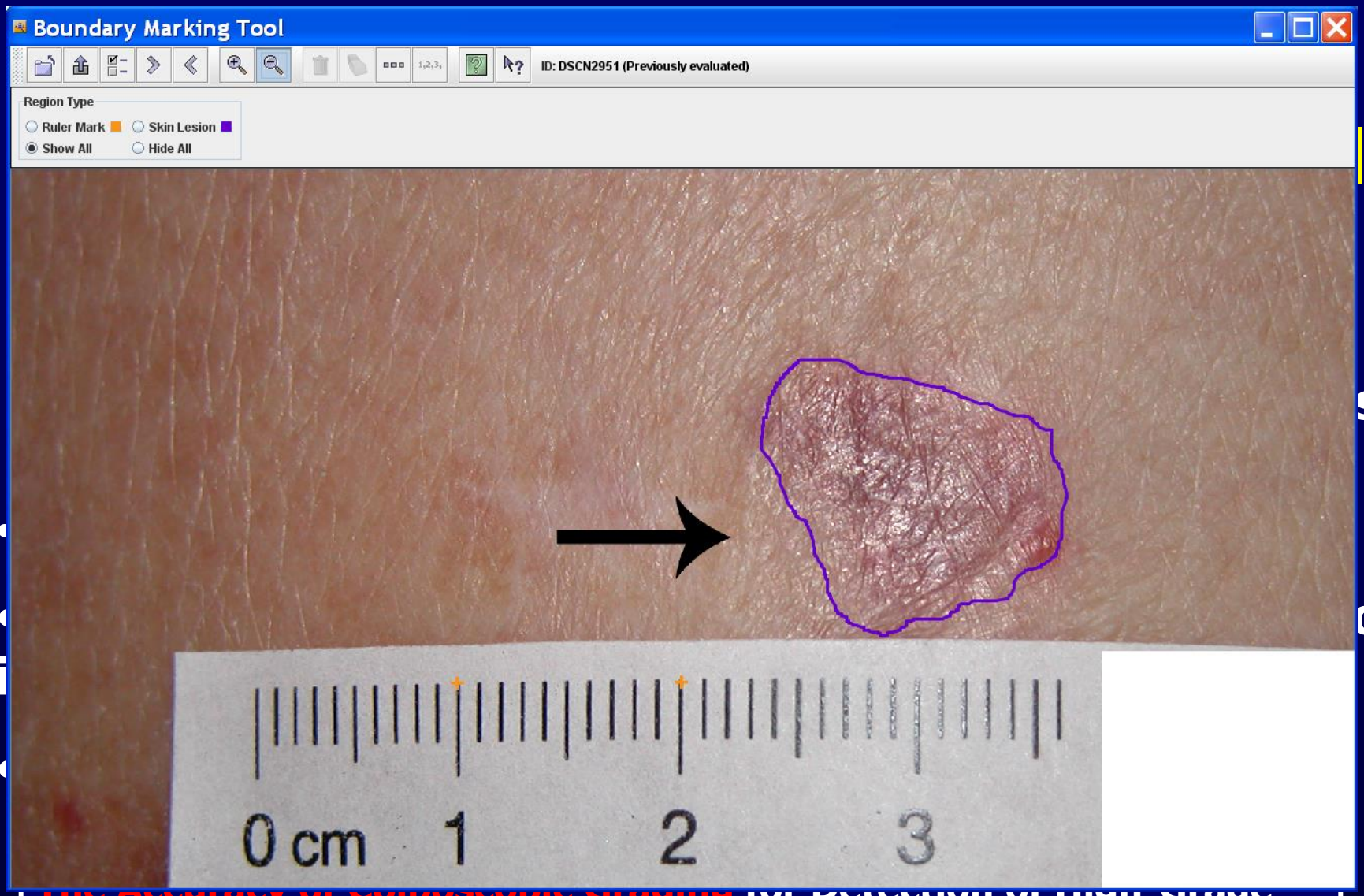
| |
|---|
| Age-Related Changes of the Cervix Influence Human Papillomavirus Type Distribution. *Cancer Research. January 2006;66(2):1218-24.* |
| Colposcopy at a Crossroads. *American Journal of Obstetrics and Gynecology. August 2006; 195(2):349-53.* |
| Interobserver agreement in the evaluation of digitized cervical images. *Obstetrics and Gynecology. 2007;110:833-40.* |
| Visual Appearance of the Uterine Cervix: Correlation With Human Papillomavirus Detection and Type. *American Journal of Obstetrics and Gynecology. July 2007;197(1):47.e1-47.e8.* |
| Interobserver Agreement in the Assessment of Components of Colposcopic Grading. *Obstetrics & Gynecology. June 2008;111(6):1279-1284.* |
| The Accuracy of Colposcopic Grading for Detection of High-Grade Cervical Intraepithelial Neoplasia. *Journal of Lower Genital Tract Disease*. 2009;13(3):137-144. |

# Other Notable System Errors Attributable to Software

USS Yorktown – Sept. 21, 1997
Divide-by-zero error stops all propulsion systems
3 hours to attach emergency engine controls
2 days to get rid of the zero, repair the engines



Mars Climate Orbiter – Sept. 23, 1999
Ground software commanded the spacecraft controls in British units; the spacecraft was designed to expect metric units.
It was lost and presumed destroyed as it was inserted into orbit around Mars.




s:

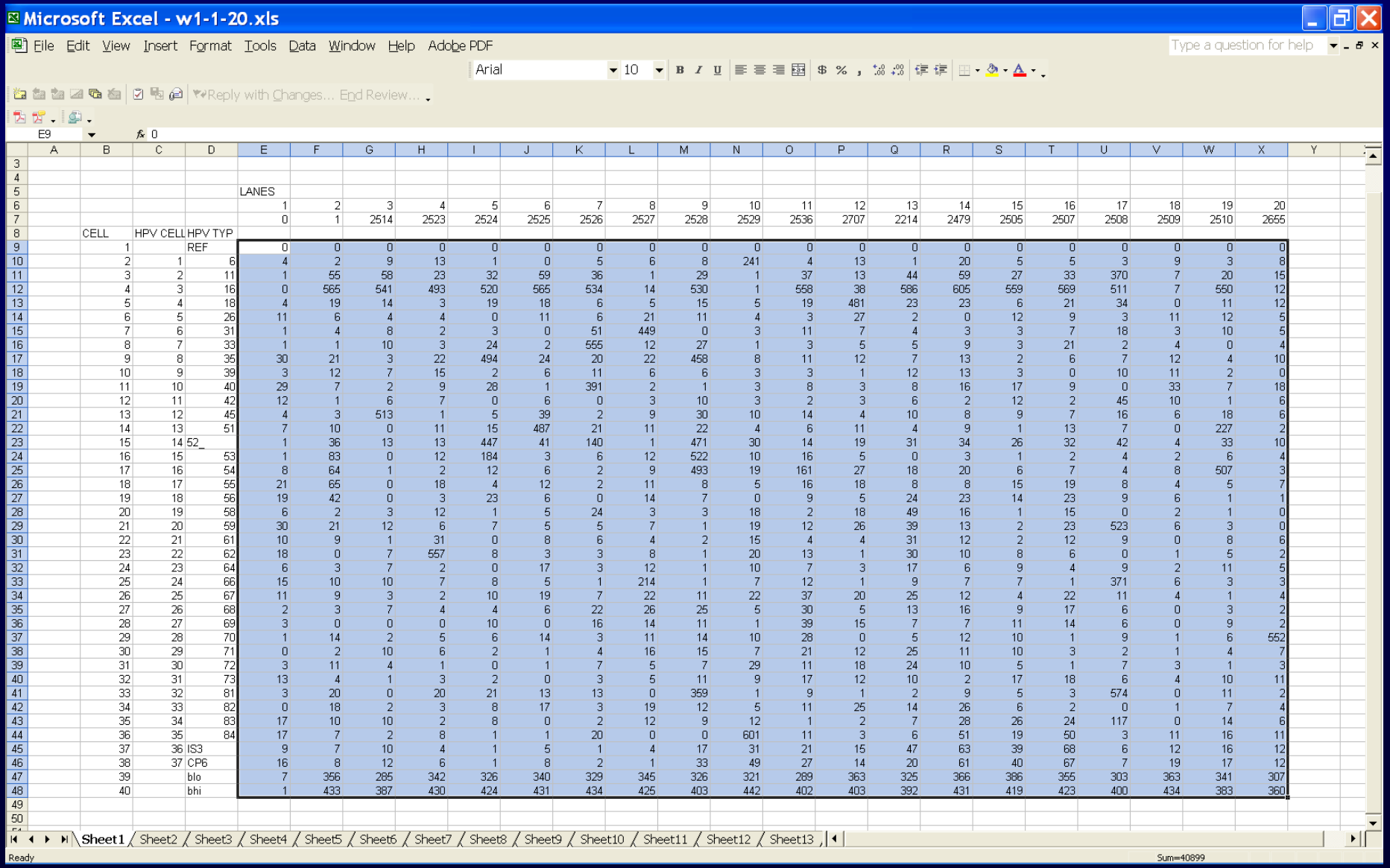
or

Treatment of Classic Kaposi Sarcoma with a Nicotine Dermal Patch: A Phase II Clinical Trial.

*Journal of Lower Genital Tract Disease*. 2009;13(3):137-144.

*Journal of the European Academy of Dermatology and Venereology. September 2008;22(9):1101-9.*

**Primary developer: Leif Neve**




| | | | | LANES | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| | | | | 0 | 1 | 2514 | 2523 | 2524 | 2525 | 2526 | 2527 | 2528 | 2529 | 2536 | 2707 | 2214 | 2479 | 2505 | 2507 | 2508 | 2509 | 2510 | 2655 |
| | CELL | HPV CELL | HPV TYP | | | | | | | | | | | | | | | | | | | | |
| | 1 | | REF | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2 | 1 | 6 | 4 | 2 | 9 | 13 | 1 | 0 | 5 | 6 | 8 | 241 | 4 | 13 | 1 | 20 | 5 | 5 | 3 | 9 | 3 | 8 |
| | 3 | 2 | 11 | 1 | 55 | 58 | 23 | 32 | 59 | 36 | 1 | 29 | 1 | 37 | 13 | 44 | 59 | 27 | 33 | 370 | 7 | 20 | 15 |
| | 4 | 3 | 16 | 0 | 565 | 541 | 493 | 520 | 565 | 534 | 14 | 530 | 1 | 558 | 38 | 586 | 605 | 559 | 569 | 511 | 7 | 550 | 12 |
| | 5 | 4 | 18 | 4 | 19 | 14 | 3 | 19 | 18 | 6 | 5 | 15 | 5 | 19 | 481 | 23 | 23 | 6 | 21 | 34 | 0 | 11 | 12 |
| | 6 | 5 | 26 | 11 | 6 | 4 | 4 | 0 | 11 | 6 | 21 | 11 | 4 | 3 | 27 | 2 | 0 | 12 | 9 | 3 | 11 | 12 | 5 |
| | 7 | 6 | 31 | 1 | 4 | 8 | 2 | 3 | 0 | 51 | 449 | 0 | 3 | 11 | 7 | 4 | 3 | 3 | 7 | 18 | 3 | 10 | 5 |
| | 8 | 7 | 33 | 1 | 1 | 10 | 3 | 24 | 2 | 555 | 12 | 27 | 1 | 3 | 5 | 5 | 9 | 3 | 21 | 2 | 4 | 0 | 4 |
| | 9 | 8 | 35 | 30 | 21 | 3 | 22 | 494 | 24 | 20 | 22 | 458 | 8 | 11 | 12 | 7 | 13 | 2 | 6 | 7 | 12 | 4 | 10 |
| | 10 | 9 | 39 | 3 | 12 | 7 | 15 | 2 | 6 | 11 | 6 | 6 | 3 | 3 | 1 | 12 | 13 | 3 | 0 | 10 | 11 | 2 | 0 |
| | 11 | 10 | 40 | 29 | 7 | 2 | 9 | 28 | 1 | 391 | 2 | 1 | 3 | 8 | 3 | 8 | 16 | 17 | 9 | 0 | 33 | 7 | 18 |
| | 12 | 11 | 42 | 12 | 1 | 6 | 7 | 0 | 6 | 0 | 3 | 10 | 3 | 2 | 3 | 6 | 2 | 12 | 2 | 45 | 10 | 1 | 6 |
| | 13 | 12 | 45 | 4 | 3 | 513 | 1 | 5 | 39 | 2 | 9 | 30 | 10 | 14 | 4 | 10 | 8 | 9 | 7 | 16 | 6 | 18 | 6 |
| | 14 | 13 | 51 | 7 | 10 | 0 | 11 | 15 | 487 | 21 | 11 | 22 | 4 | 6 | 11 | 4 | 9 | 1 | 13 | 7 | 0 | 227 | 2 |
| | 15 | 14 | 52_ | 1 | 36 | 13 | 13 | 447 | 41 | 140 | 1 | 471 | 30 | 14 | 19 | 31 | 34 | 26 | 32 | 42 | 4 | 33 | 10 |
| | 16 | 15 | 53 | 1 | 83 | 0 | 12 | 184 | 3 | 6 | 12 | 522 | 10 | 16 | 5 | 0 | 3 | 1 | 2 | 4 | 2 | 6 | 4 |
| | 17 | 16 | 54 | 8 | 64 | 1 | 2 | 12 | 6 | 2 | 9 | 493 | 19 | 161 | 27 | 18 | 20 | 6 | 7 | 4 | 8 | 507 | 3 |
| | 18 | 17 | 55 | 21 | 65 | 0 | 18 | 4 | 12 | 2 | 11 | 8 | 5 | 16 | 18 | 8 | 8 | 15 | 19 | 8 | 4 | 5 | 7 |
| | 19 | 18 | 56 | 19 | 42 | 0 | 3 | 23 | 6 | 0 | 14 | 7 | 0 | 9 | 5 | 24 | 23 | 14 | 23 | 9 | 6 | 1 | 1 |
| | 20 | 19 | 58 | 6 | 2 | 3 | 12 | 1 | 5 | 24 | 3 | 3 | 18 | 2 | 18 | 49 | 16 | 1 | 15 | 0 | 2 | 1 | 0 |
| | 21 | 20 | 59 | 30 | 21 | 12 | 6 | 7 | 5 | 5 | 7 | 1 | 19 | 12 | 26 | 39 | 13 | 2 | 23 | 523 | 6 | 3 | 0 |
| | 22 | 21 | 61 | 10 | 9 | 1 | 31 | 0 | 8 | 6 | 4 | 2 | 15 | 4 | 4 | 31 | 12 | 2 | 12 | 9 | 0 | 8 | 6 |
| | 23 | 22 | 62 | 18 | 0 | 7 | 557 | 8 | 3 | 3 | 8 | 1 | 20 | 13 | 1 | 30 | 10 | 8 | 6 | 0 | 1 | 5 | 2 |
| | 24 | 23 | 64 | 6 | 3 | 7 | 2 | 0 | 17 | 3 | 12 | 1 | 10 | 7 | 3 | 17 | 6 | 9 | 4 | 9 | 2 | 11 | 5 |
| | 25 | 24 | 66 | 15 | 10 | 10 | 7 | 8 | 5 | 1 | 214 | 1 | 7 | 12 | 1 | 9 | 7 | 7 | 1 | 371 | 6 | 3 | 3 |
| | 26 | 25 | 67 | 11 | 9 | 3 | 2 | 10 | 19 | 7 | 22 | 11 | 22 | 37 | 20 | 25 | 12 | 4 | 22 | 11 | 4 | 1 | 4 |
| | 27 | 26 | 68 | 2 | 3 | 7 | 4 | 4 | 6 | 22 | 26 | 25 | 5 | 30 | 5 | 13 | 16 | 9 | 17 | 6 | 0 | 3 | 2 |
| | 28 | 27 | 69 | 3 | 0 | 0 | 0 | 10 | 0 | 16 | 14 | 11 | 1 | 39 | 15 | 7 | 7 | 11 | 14 | 6 | 0 | 9 | 2 |
| | 29 | 28 | 70 | 1 | 14 | 2 | 5 | 6 | 14 | 3 | 11 | 14 | 10 | 28 | 0 | 5 | 12 | 10 | 1 | 9 | 1 | 6 | 552 |
| | 30 | 29 | 71 | 0 | 2 | 10 | 6 | 2 | 1 | 4 | 16 | 15 | 7 | 21 | 12 | 25 | 11 | 10 | 3 | 2 | 1 | 4 | 7 |
| | 31 | 30 | 72 | 3 | 11 | 4 | 1 | 0 | 1 | 7 | 5 | 7 | 29 | 11 | 18 | 24 | 10 | 5 | 1 | 7 | 3 | 1 | 3 |
| | 32 | 31 | 73 | 13 | 4 | 1 | 3 | 2 | 0 | 3 | 5 | 11 | 9 | 17 | 12 | 10 | 2 | 17 | 18 | 6 | 4 | 10 | 11 |
| | 33 | 32 | 81 | 3 | 20 | 0 | 20 | 21 | 13 | 13 | 0 | 359 | 1 | 9 | 1 | 2 | 9 | 5 | 3 | 574 | 0 | 11 | 2 |
| | 34 | 33 | 82 | 0 | 18 | 2 | 3 | 8 | 17 | 3 | 19 | 12 | 5 | 11 | 25 | 14 | 26 | 6 | 2 | 0 | 1 | 7 | 4 |
| | 35 | 34 | 83 | 17 | 10 | 10 | 2 | 8 | 0 | 2 | 12 | 9 | 12 | 1 | 2 | 7 | 28 | 26 | 24 | 117 | 0 | 14 | 6 |
| | 36 | 35 | 84 | 17 | 7 | 2 | 8 | 1 | 1 | 20 | 0 | 0 | 601 | 11 | 3 | 6 | 51 | 19 | 50 | 3 | 11 | 16 | 11 |
| | 37 | 36 | IS3 | 9 | 7 | 10 | 4 | 1 | 5 | 1 | 4 | 17 | 31 | 21 | 15 | 47 | 63 | 39 | 68 | 6 | 12 | 16 | 12 |
| | 38 | 37 | CP6 | 16 | 8 | 12 | 6 | 1 | 8 | 2 | 1 | 33 | 49 | 27 | 14 | 20 | 61 | 40 | 67 | 7 | 19 | 17 | 12 |
| | 39 | | blo | 7 | 356 | 285 | 342 | 326 | 340 | 329 | 345 | 326 | 321 | 289 | 363 | 325 | 366 | 386 | 355 | 303 | 363 | 341 | 307 |
| | 40 | | bhi | 1 | 433 | 387 | 430 | 424 | 431 | 434 | 425 | 403 | 442 | 402 | 403 | 392 | 431 | 419 | 423 | 400 | 434 | 383 | 360 |