

# CYTOLOGY PROFICIENCY TESTING AND NEW TECHNOLOGIES IN CERVICAL CANCER SCREENING

George G. Birdsong, M.D.  
Emory University School of Medicine  
Grady Health System

Clinical Laboratory Improvement Advisory Committee Meeting  
June 20, 2006  
Atlanta, GA

I would like to acknowledge and thank Cytyc Corp. and TriPath Imaging, Inc. for their assistance in the preparation of slides used in this talk

# TriPath Products

## Current

- SurePath<sup>®</sup> liquid-based Pap test
- FocalPoint<sup>®</sup> slide profiler
- ProEx C (ASR) – Analyte Specific Reagent to detect the over expression of proteins associated with aberrant S-Phase induction

## Future\*

- FocalPoint Guided Screening (GS) Imaging System\*

\* Investigational Use Only, Not for sale in the US

## TriPath Products – Focal Point Slide Profiler

- Automated computerized primary screening system
- FDA approved 1998 (Conventional) & 2001 (SurePath)
- Ranks and sorts slides based on the probability of abnormality
- Uses algorithms (squamous and glandular) to assess cell changes
- Assesses adequacy
- Archives up to 25% of slides most likely to be NILM
  - (i.e. not seen by humans)
- Customized to laboratory's stain and patient population (disease prevalence)
- Selects 15% of qualified NILM slides for a directed QC Rescreen which replaces the random 10% selection

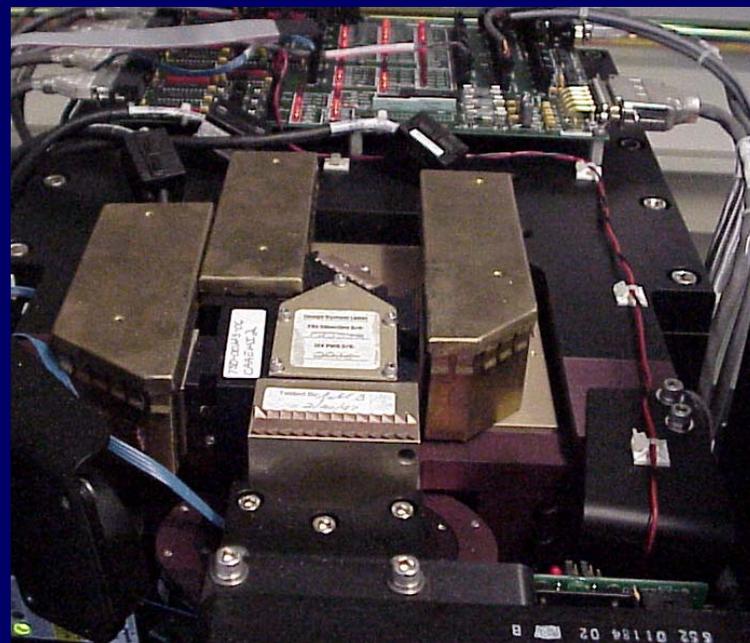
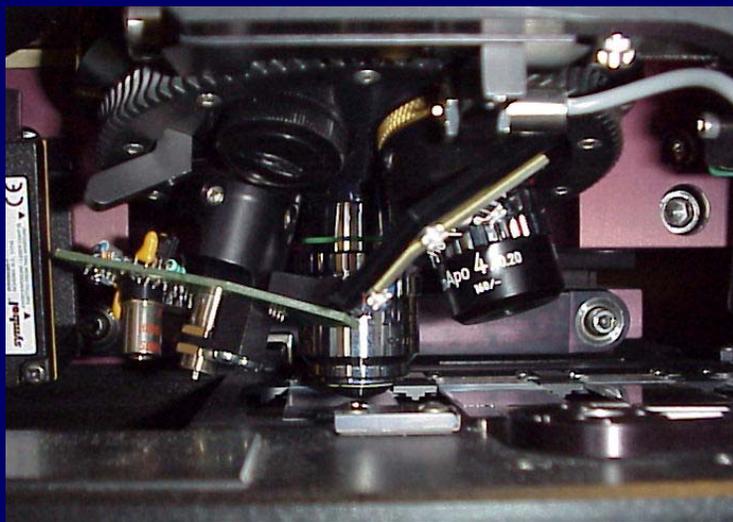
# FocalPoint Guided Screening System\*

- Automated primary screening system
- Ranks and sorts slides based on the probability of abnormality
- Uses algorithms (squamous and glandular) to assess cell changes and sample adequacy
- Customized to laboratory stain and patient population
- Directed QC Rescreen of 15% of qualified slides to replace random 10% selection
- Up to x # Fields of View (FOV) for each SurePath slide are presented to the cytotechnologist for screening.
- Screening takes place at the GS Review Station

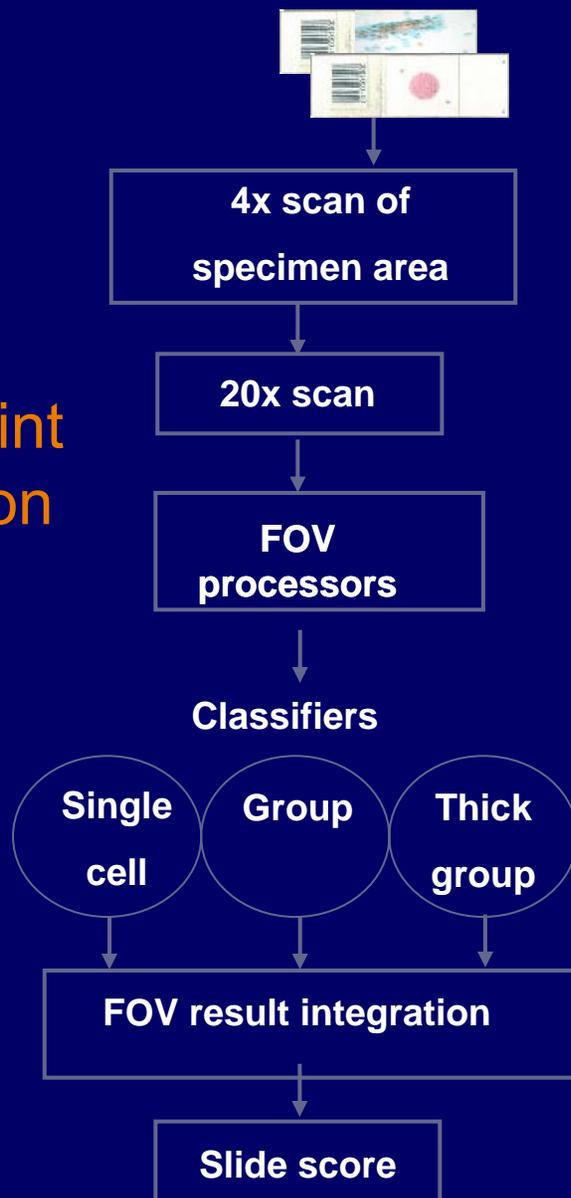
\* Not available for sale in the United States, Investigational Use Only

# FOCALPOINT™

*slide profiler*



# FocalPoint Operation



Slide: SurePath® / Conventional

Selection of 1000 fields for in-depth analysis

High resolution field of view scan of selected images

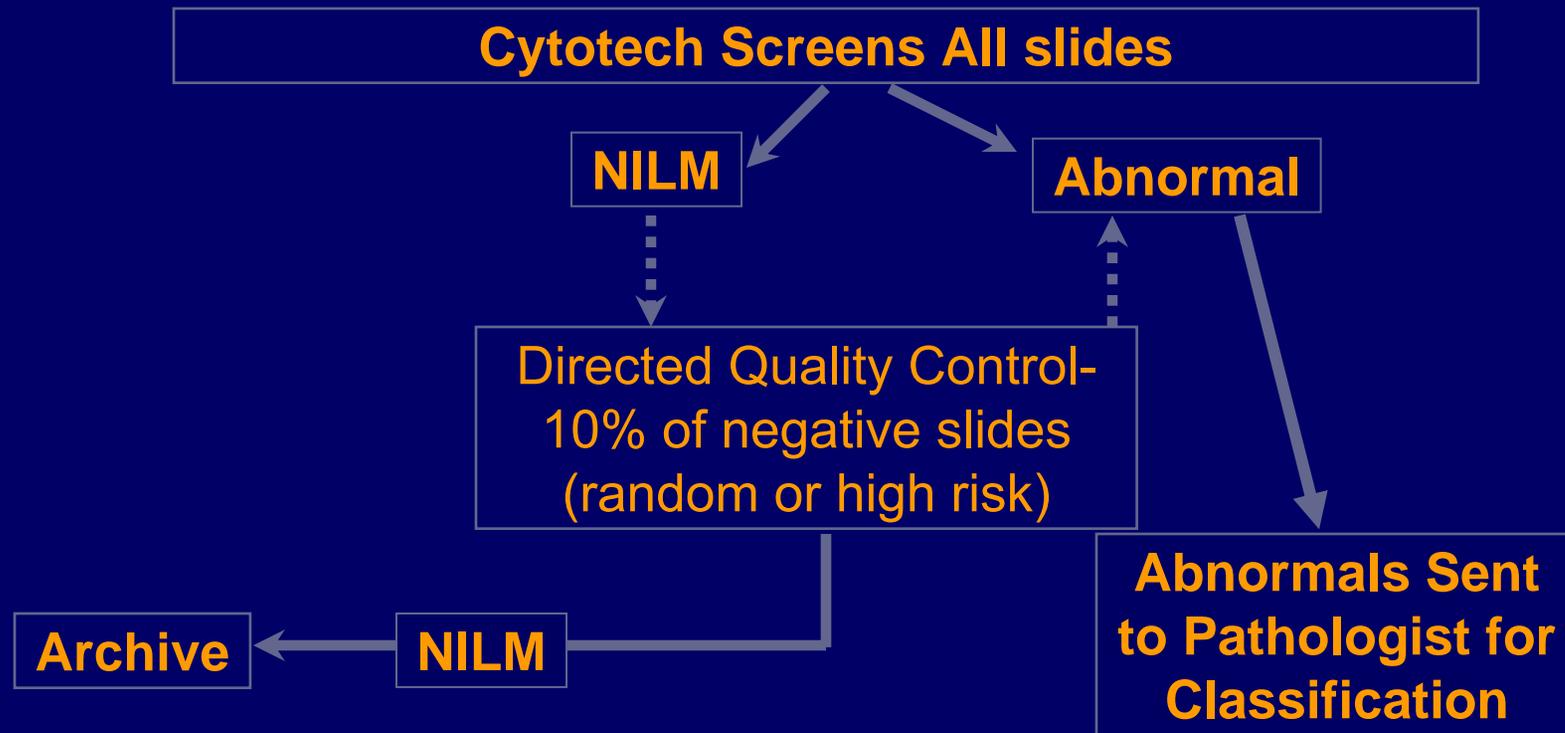
Feature description of single objects, groups and thick groups

Single cell, group and thick group score values for each field of view (FOV)

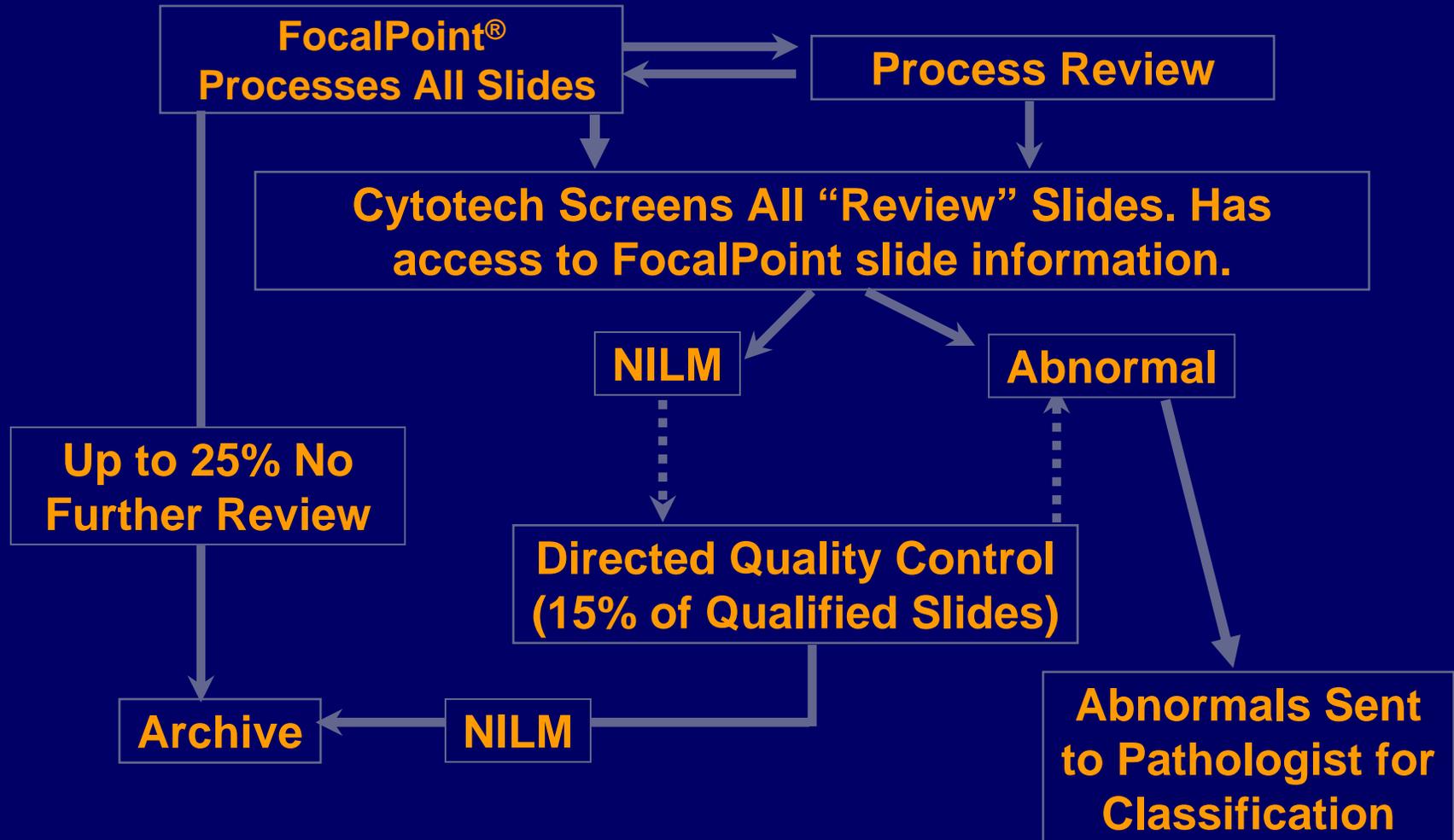
FOV result accumulation and integration

Slide score value between 0 and 1.0

# Traditional Cytology Lab Work Flow

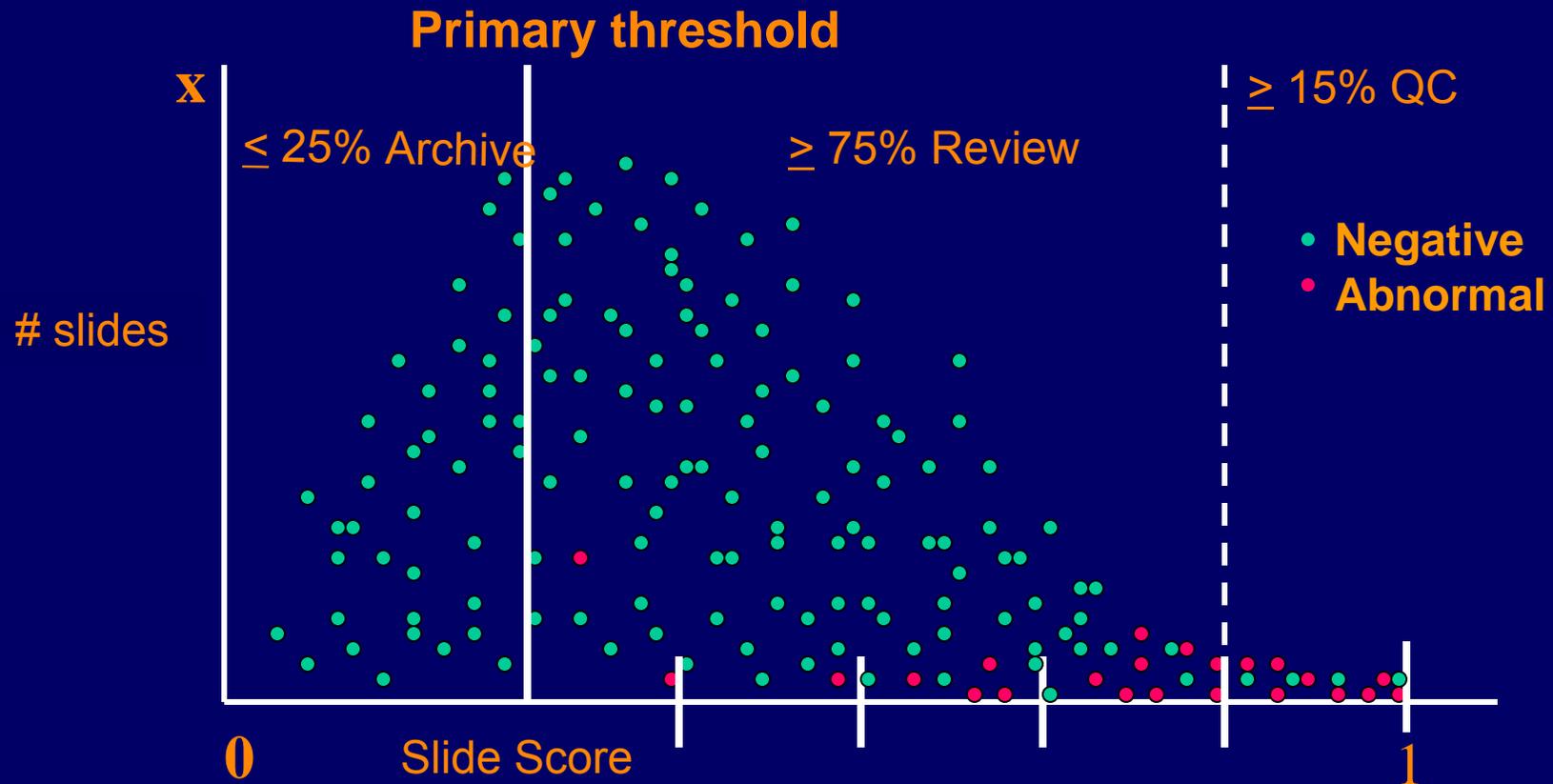


# FocalPoint Profiler Normal Work Flow



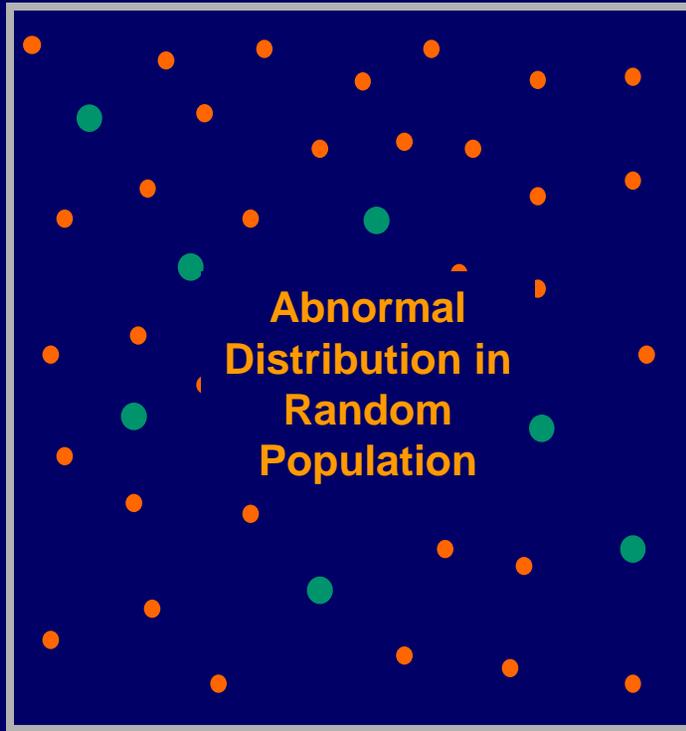
# SORTING & RANKING (ILLUSTRATION)

The FocalPoint SORTS and RANKS slides based on the likelihood of abnormality being present. 0 = Negative ,1 = Abnormal



# ENRICHED QC POPULATION CONCEPT MODEL

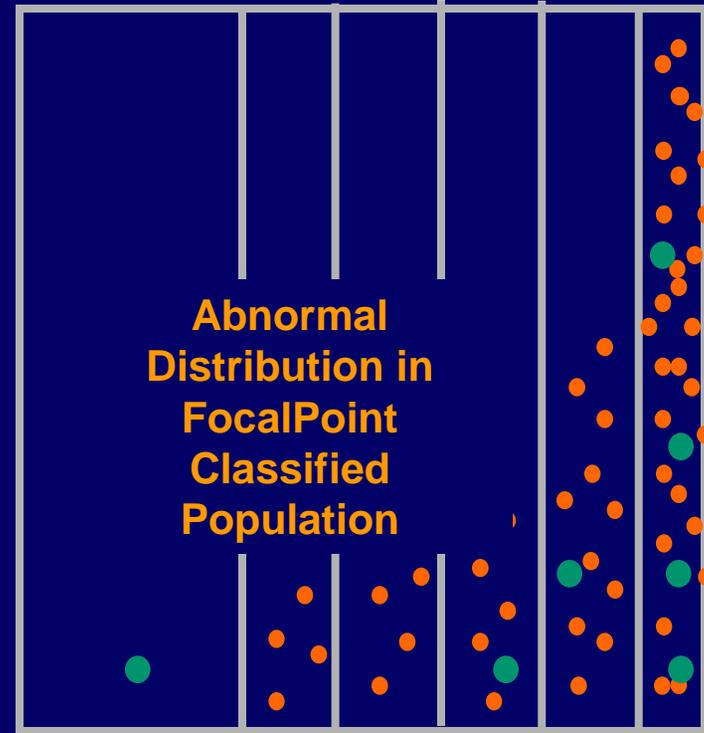
**Manual Practice\***  
**Random QC selection**



● = false-negatives

10% Random Rescreening

**FocalPoint Assisted Practice**  
**Enriched QC selection**



FNs

Q5

Q4

Q3

Q2

Q1

25% No Further Review

≥ 75% Review

## SLIDE RANKING : SUREPATH® SLIDES

Diagnosis	Quintile 1*	Quintile 1 & 2**
ASCUS/AGUS	41%	65%
LSIL	51%	71%
HSIL	63%	80%
HSIL <sup>+</sup>	63%	81%
AIS	0%	100%
Cancer	65%	91%
Total (ASCUS+)	50%	72%

## FocalPoint Guided Screening System\*

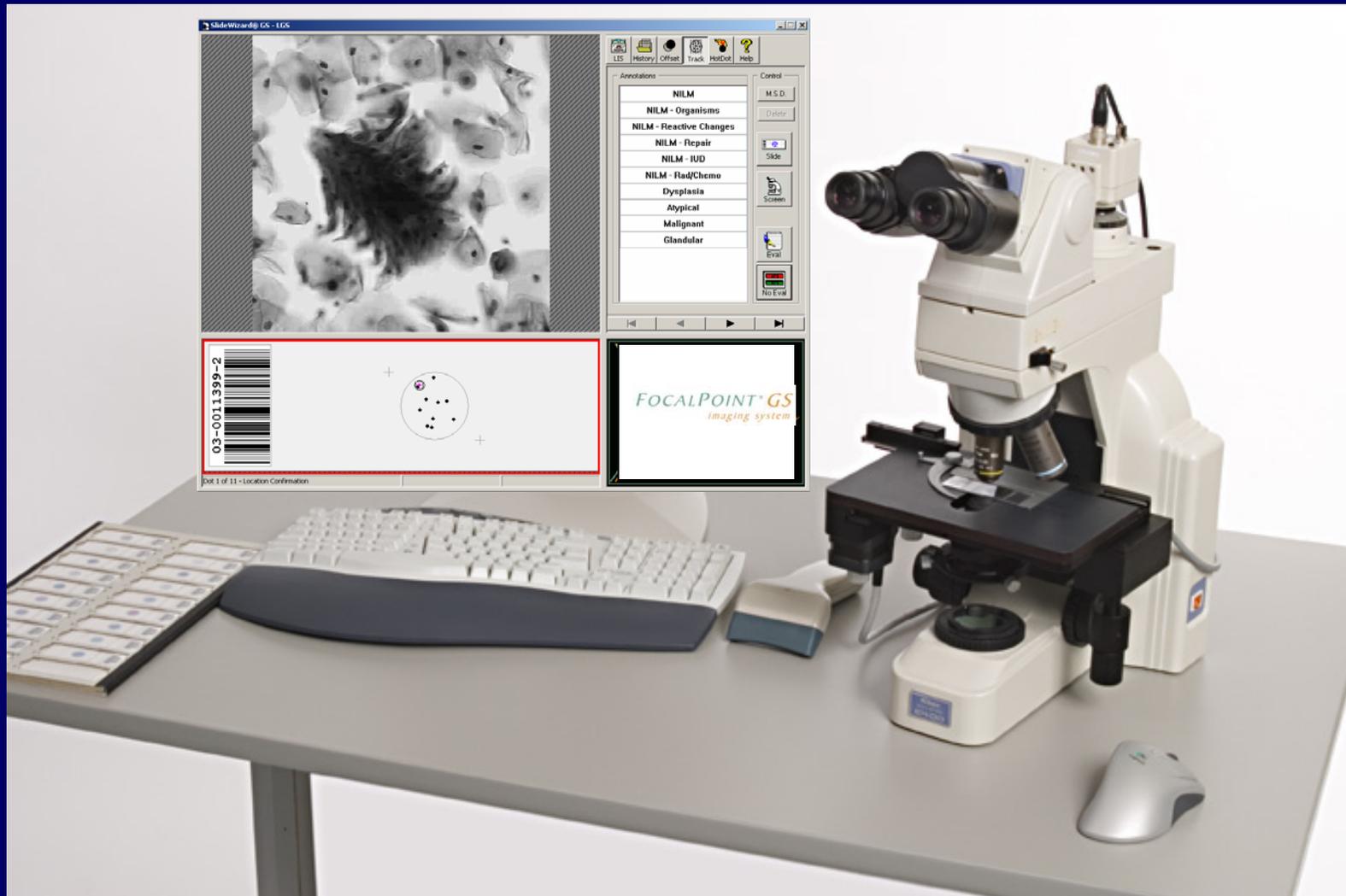
- Automated primary screening system
- Ranks and sorts slides based on the probability of abnormality
- Uses algorithms (squamous and glandular) to assess cell changes and sample adequacy
- Customized to laboratory stain and patient population
- Directed QC Rescreen of 15% of qualified slides to replace random 10% selection

\* Not available for sale in the United States

## FocalPoint Guided Screening System\*

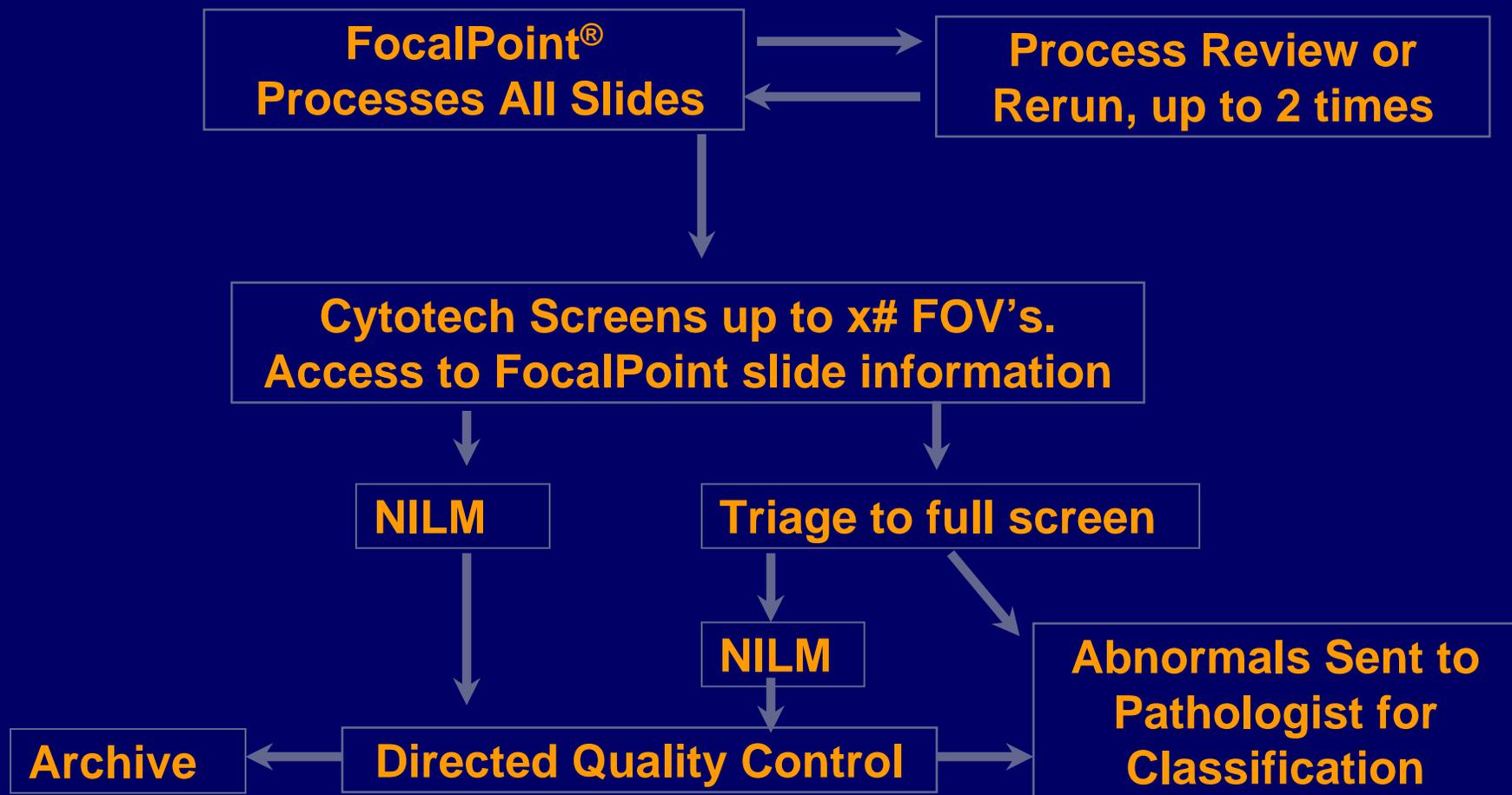
- Up to x # Fields of View (FOV) for each SurePath slide are presented to the cytotechnologist for screening.
- Screening takes place at the GS Review Station
- If NILM on up to x # FOVs → sign out
- If suspicious or abnormal → full slide review

\* Not available for sale in the United States



Not available for sale in the United States

# FocalPoint GS Imaging System: \* Normal Work Flow



\* Investigational Use Only, Not for sale in the US

# ThinPrep Imaging System: Historical Background

- ThinPrep Pap Test FDA approved in May, 1996
- ThinPrep Imaging System (TIS) received FDA approval in June, 2003

# ThinPrep Imaging System

- Interactive Imaging System
  - Combines computer assisted primary screening with human expertise
- Increases productivity and sensitivity\*

*\*ASCUS+ (Reference: ThinPrep Imaging System Operation Summary and Clinical Information)*

# ThinPrep Imaging System: Perspective

- Approximately 35 million ThinPrep Pap Tests are performed annually in the United States
- As March 2006 there were 334 ThinPrep Imaging systems in use in the United States
- Approximately 30% of ThinPrep Slides are examined with the ThinPrep Imaging System

# ThinPrep Imaging System

- Utilizes proprietary stain (ThinPrep Stain), which is visually similar to conventional stain
  - Reduces variability of stain intensity
  - Nuclear stain intensity quantitatively related to DNA content of nucleus
  - Staining protocol designed to work the TIS algorithms

# ThinPrep Imaging System

- Image Processor:
  - PC based, expandable, “networkable”
  - 300 slides/day throughput
  - Identifies 22 “fields of view” which contain objects of interest
  - Automated review scope used by cytotechnologist for screening interpretation and slide marking

# Review Scope

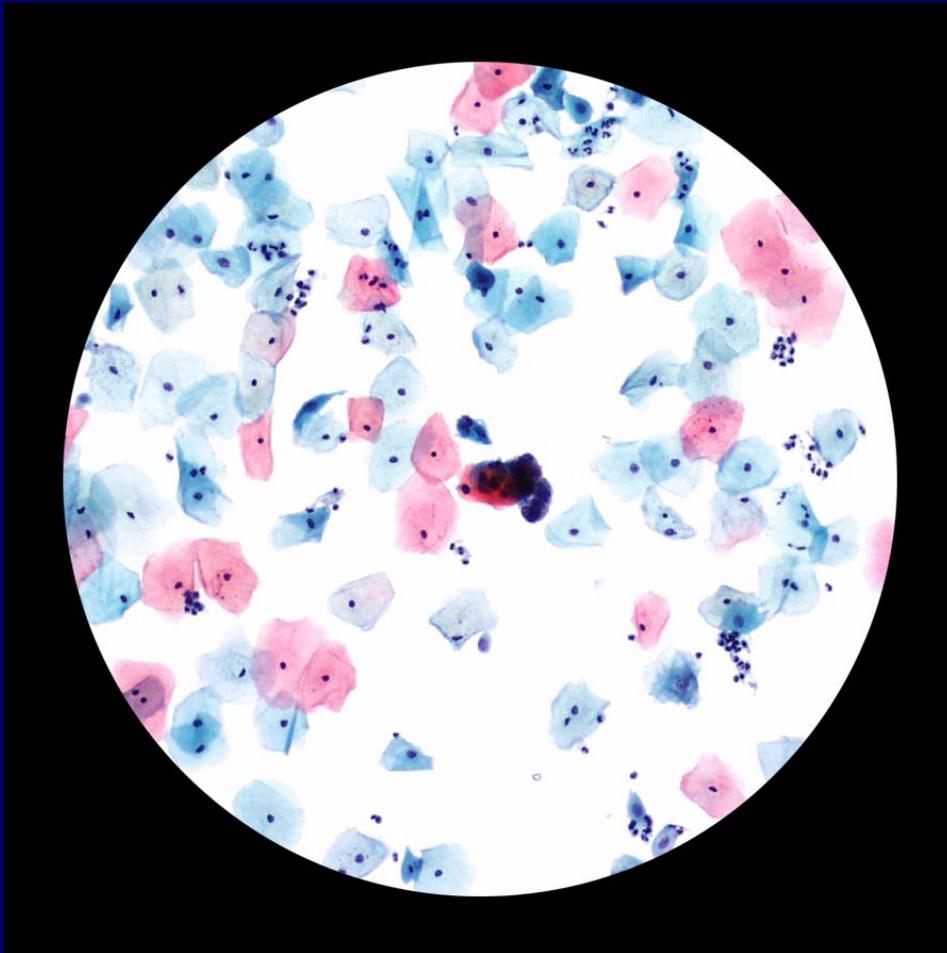
## Technical Design

- Standard Microscope Optics With Proprietary Cytoc - Designed Stage
- User Programmable Screening Preferences
  - Scanning direction
  - Speed
  - AutoScan™ mode
- Electronic Marking And Unmarking Capabilities
  - Only mark fields requiring pathologist review
  - Precision Slide “L” Marking

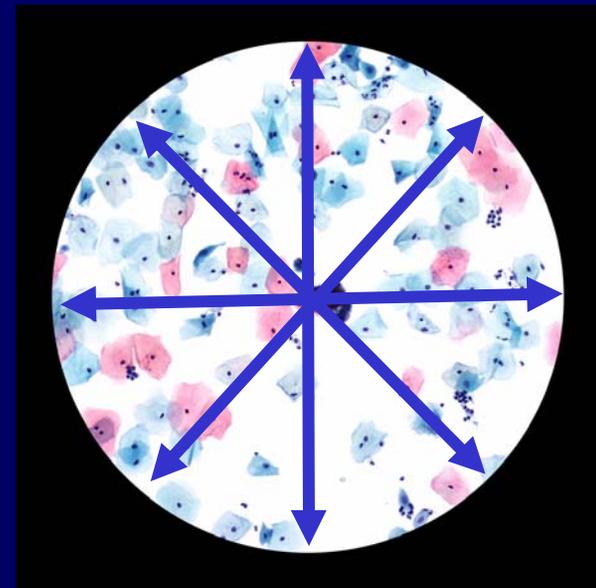
# Optical Cellular Selection(OCS) Algorithms

- Algorithms look for the largest, darkest objects (increased DNA)
- Algorithms analyze both single cells and clusters; overlapping nuclei are excluded
- A minimum of 2/22 FOV's are presented representing clusters of cells
- Remainder of FOV's present predominantly single cells if available on the slide

# Field of View Screening



*Cytotechnologists  
responsible for  
entire FOV*



## Field of View Screening

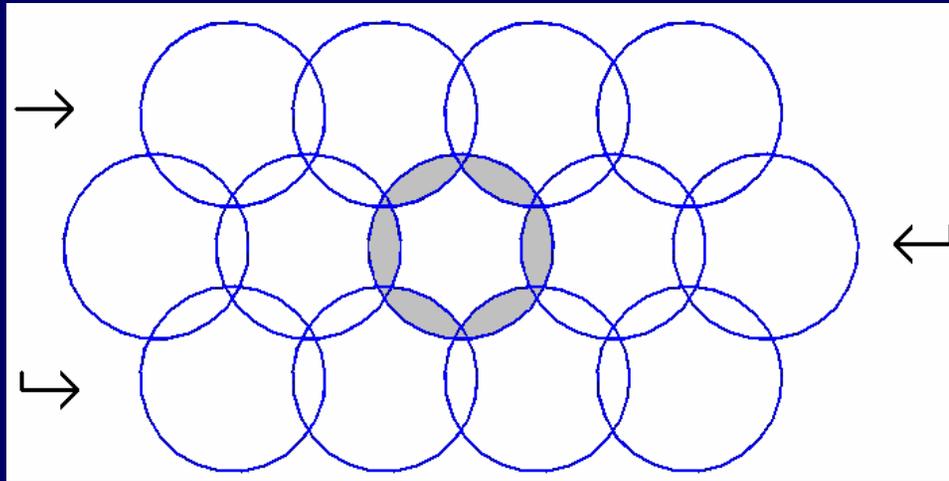
- Imaging system locates cells of interest
- Cytotechnologist determines diagnosis and specimen adequacy
  - During 22 FOV review
  - 23<sup>rd</sup> FOV = 12 o'clock position
    - For diagonal adequacy review
  - Locate endocervical component
  - Determine infectious agents

# AutoScan™ Mode

- If any FOV is electronically marked the entire slide is reviewed by the cytotechnologist on the review scope
- Simulates Manual Screening
  - Variety of scanning modes
    - Continuous
    - Auto Start/Stop
    - User Start/Stop



# Field of View Overlap



- Shaded area = approximately 50%
- Programmed to ensure 100% of cell spot is presented to screener

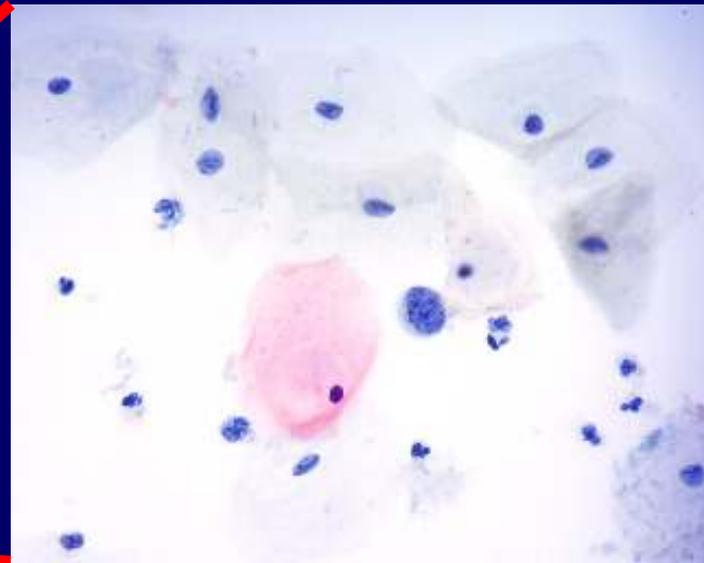
# FOV Screening vs Traditional Manual Screening

## Different From Manual Screening

- Physical Modifications
  - Manual screening moves the slide resulting in minimal eye movement
  - FOV screening requires movement of your eyes to review entire area
- Thought Process Modifications
  - Low degrees of cellular atypia and even one slightly atypical cell should trigger autoscan
  - Reactive cellular changes should also trigger autoscan
- Screen all 22 FOV's – clinical trial supports increased pickup of disease using imager to assist with CT locator skills

# Dotted slides passed to the Pathologist

*10x*

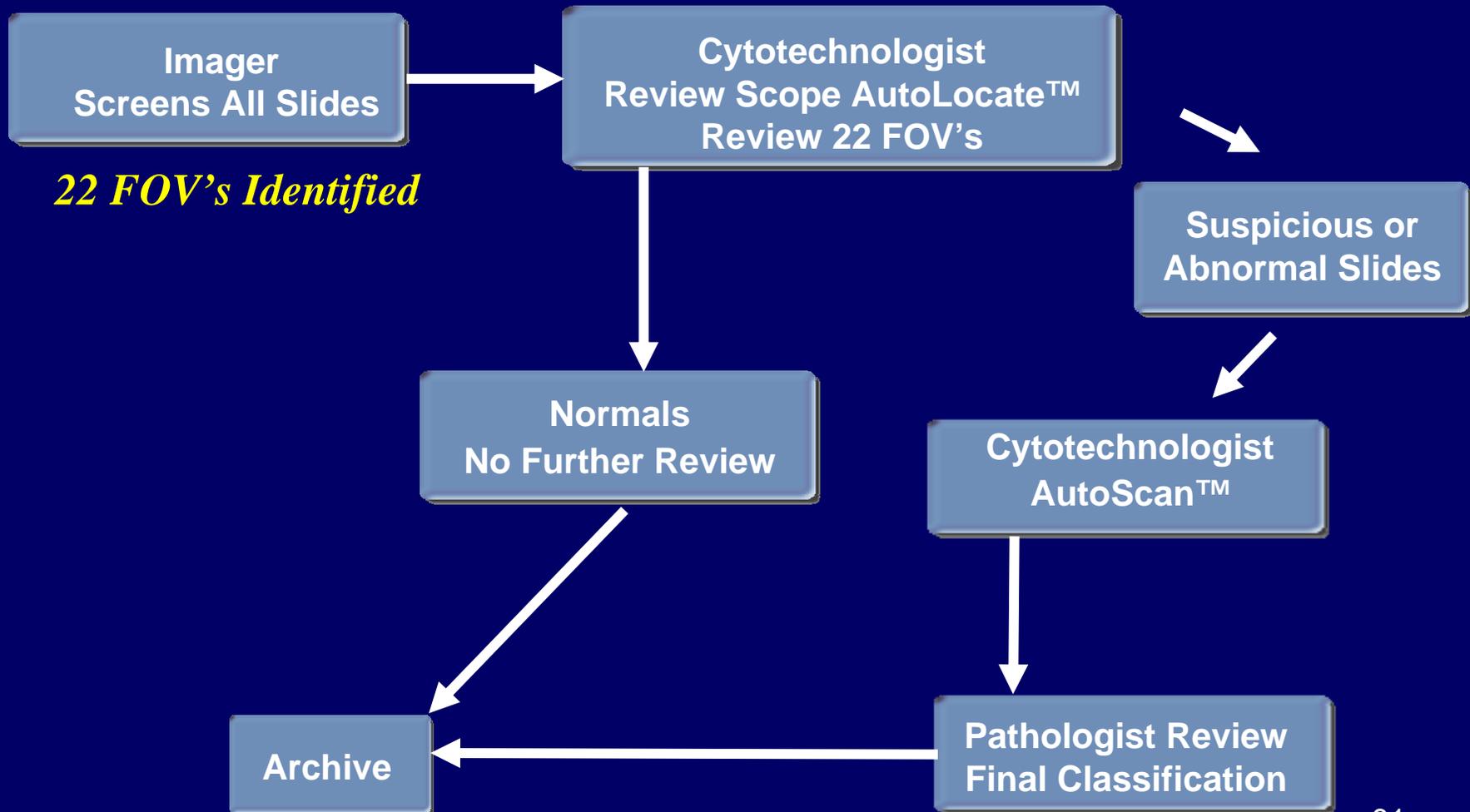


*40x*

# Summary: Cytotechnologist Review

- Every Slide Is Reviewed By A Cytotechnologist
  - Normal or Abnormal
- Utilizes Proprietary Features Of The Review Scope
  - AutoLocate™ – Review 22 FOV's
    - Normal - review 22 FOV's, no further review required
    - Abnormal - mark fields and AutoScan
  - AutoScan™ – automatically review the entire slide
  - Precision Slide “L” Marking

# Cytotechnologist Workflow



# Reduction in Slide Screening Time

**Example: Cytotechnologist screening 80 slides/day**

80 Slides x 120 FOV =  
9600 FOV

TOTAL: 9600  
FOV's/day

80 Slides x 22 FOV =  
1760 FOV

(10%) Abnormals)

8 Slides x 120 FOV =

960 FOV

TOTAL: 2720  
FOV's/day

*In this example, ThinPrep Imager screening could result in a 71.6% reduction in the total area screened.*

## Additional Benefits of Imaging Directed™ Cytology

- Effectively Utilize CT's Superior Interpretive Skills
  - Focus on areas of diagnostic relevance and spend time required to accurately diagnose
- A standardized approach to screening
- Standardized slide marking simplifies Pathologist review
- Potential reduction in false-negative fraction  
(Individual lab performance may vary)

# Liquid Based Paps

- ThinPrep Pap test
  - ThinPrep Imaging System
- SurePath Pap test
  - FocalPoint slide profiler
- MonoPrep LBP system (FDA approved 3/06)
  - Image analysis and molecular tests under development

# Liquid Based Paps



Representative  
Homogenous  
Sample

SurePath™ Slide



# Liquid Based Paps

- The three preparations have somewhat different morphology
- PT providers maintain separate sets of ThinPrep and SurePath slides
- MonoPrep too new
  - Probable 4-5 year lag time for PT providers to have a sufficient quantity of slides to offer MonoPrep PT slides

## Molecular Testing

- Digene Hybrid Capture 2
  - Tests for 13 high risk types of Human Papillomavirus
- FDA approved for ASC-US triage
- FDA approved for co-testing of women 30 or over
- PT with clinical lab paradigm

## Can PT Accommodate This New Technology ?

### FocalPoint slide profiler & FocalPoint GS Imaging System

- PT slides are obtained from many contributors from different types of laboratories.
- Challenges to overcome would include:
  - Stain variability
  - Prevalence of disease
  - Barcode logistics
  - Reproducibility (yet untested)
  - For GS how does PT vendor validate FOV on test slides
  - Scoring issues: Are points deducted for triaging NILM to full slide review
  - SurePath slide volume to accommodate testing (PT vendors)

\* Not available for sale in the United States

## Can PT be applied to other new technologies?

- Preparation techniques have unique morphologic appearances
  - Conventional morphology
  - ThinPrep morphology
  - SurePath morphology
  - MonoPrep morphology
- Stain affects interpretation
- Stain fades over time, affecting interpretation

## Can PT be applied to other new technologies?

- Imager assisted screening  $\neq$  manual screening
- Many cytotechnology students and pathology residents see mostly one type of Pap test, and see few, or no conventional Pap smears during their training

## Can PT be applied to other new technologies?

- Multiple slides can be prepared from a vial, or from pooled material
- But, there will be inter- and intra-observer interpretive variability



## Can PT be applied to other new technologies?

- FocalPoint product labeling is based on laboratory performance data (manual practice vs FocalPoint assisted practice) not individual performance
- However, FocalPoint Directed QC Re-screen may identify poor performers (individual)
- Automation impacts overall lab practice and it may be difficult to test an individual's screening and interpretation competencies on a small subset of slides i.e. 10 slide PT test
- An individual's competency is assessed using multiple parameters trended over time with or without automation

## Can PT be applied to other new technologies?

- Neither imager was designed to accommodate multiple scans of the same slide
- FDA approval required to modify software

# CYTOLOGY PROFICIENCY TESTING AND NEW TECHNOLOGIES IN CERVICAL CANCER SCREENING

QUESTIONS?