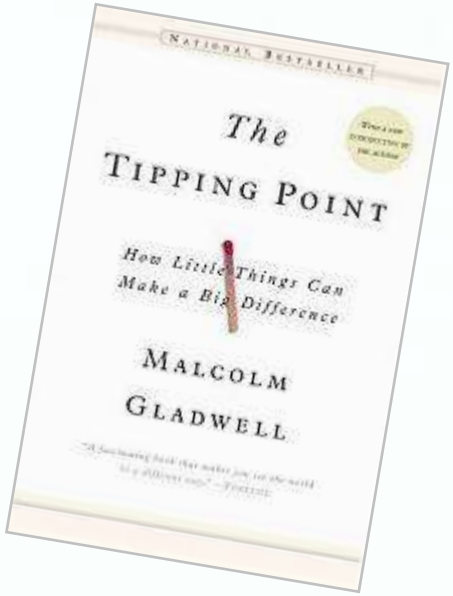
Virtual Microscopy:
A Tipping Point in Tissue Based Research and Education

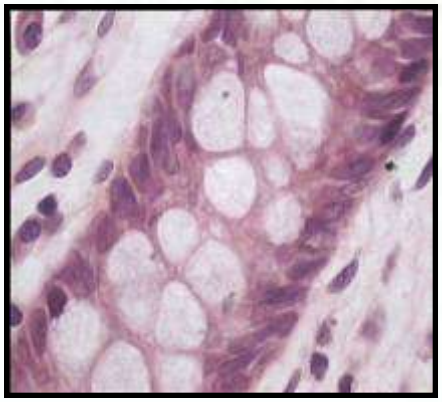
James Diamond
Peter Hamilton
Queen's University of Belfast

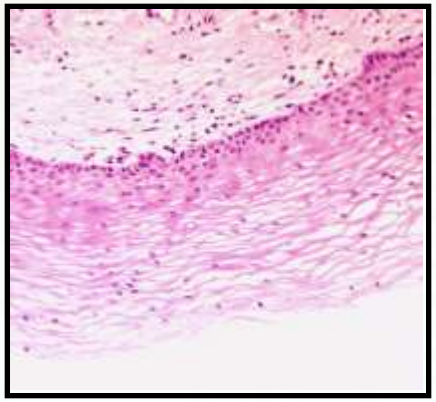


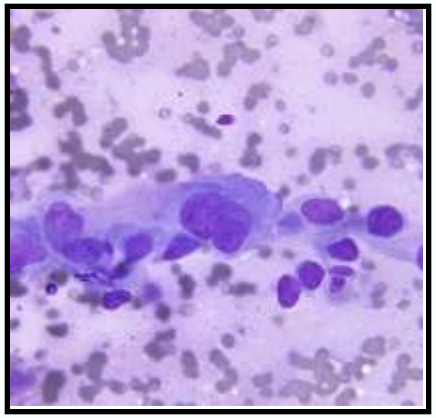
Queen's University Belfast

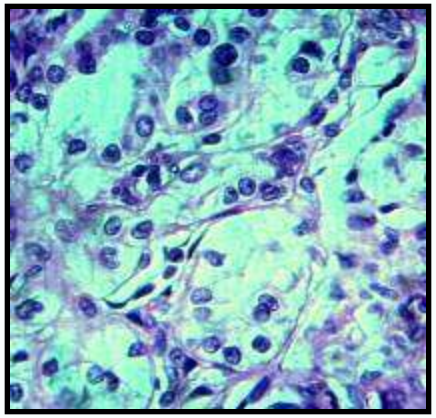
Pathology

Skilled interpretation of tissue morphology
Pathology diagnostics is central to patient care

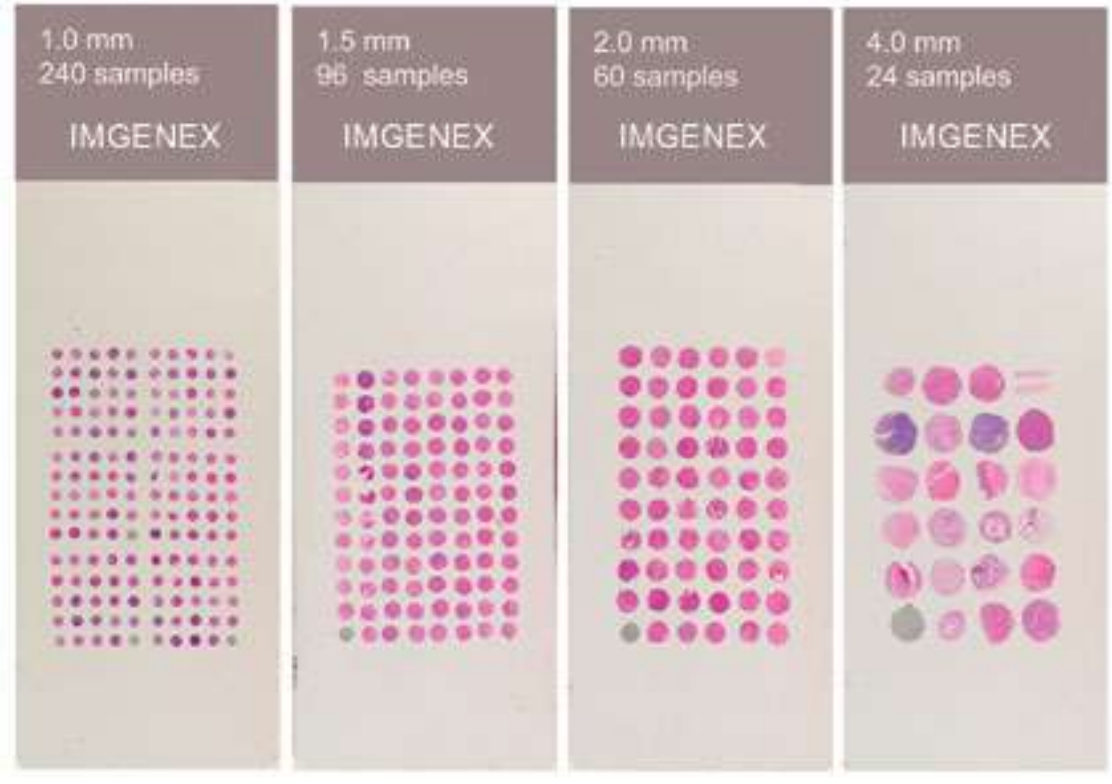




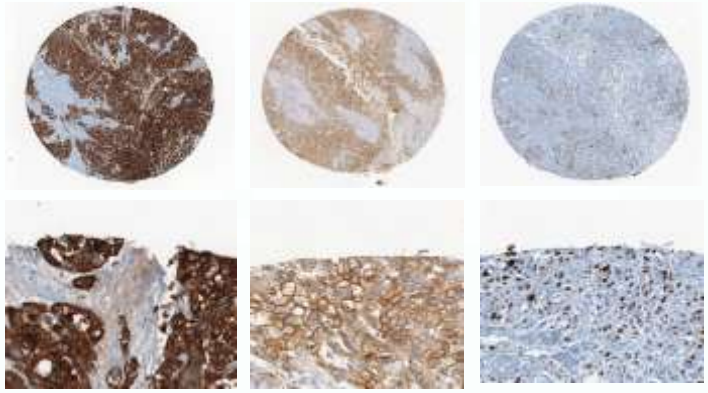




Pathology diagnostics is central to translational research and biomarker discovery

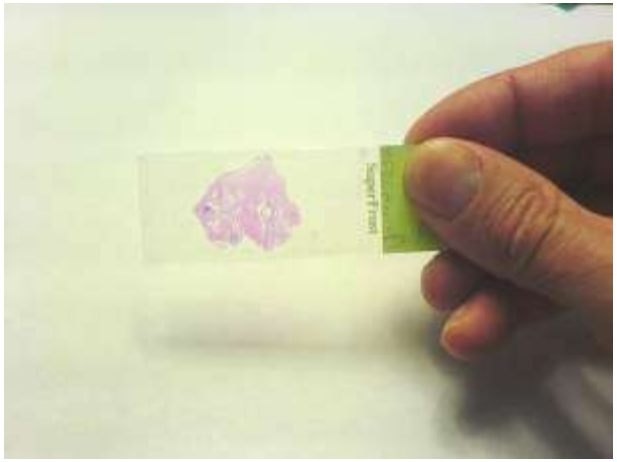


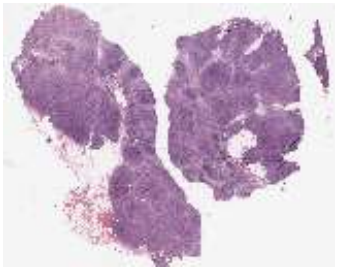
(Courtesy of Imgenex)



AE1AE3 E-Cadherin Ki67

The Tipping Point ?
Turning glass slides into bits and bytes





Hardware – a competitive market

HAMAMATSU

APPLIED IMAGING

CLARIENT

Olympus .slide

Nikon CoolScope & BLISS

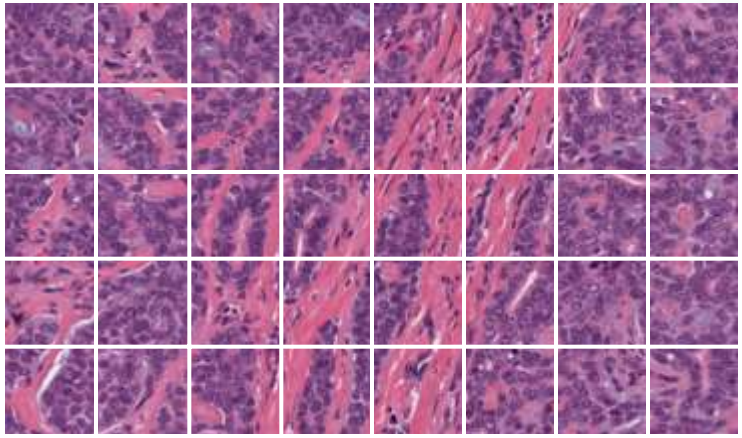
d·metrix

Aperio TECHNOLOGIES

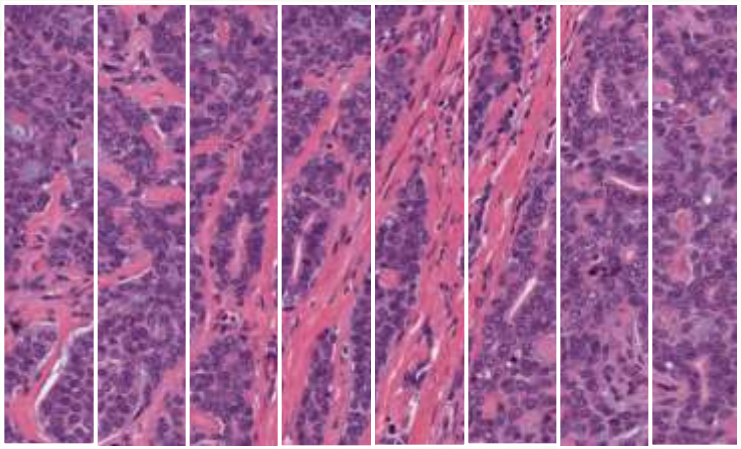
ZEISS

Single objective

Image tiling

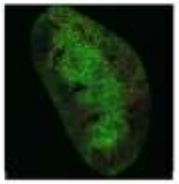


Line scanning

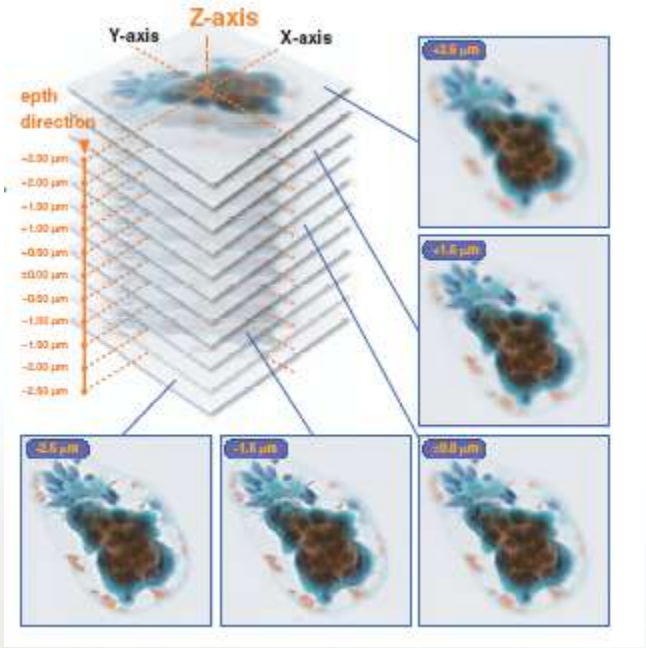


The array microscope

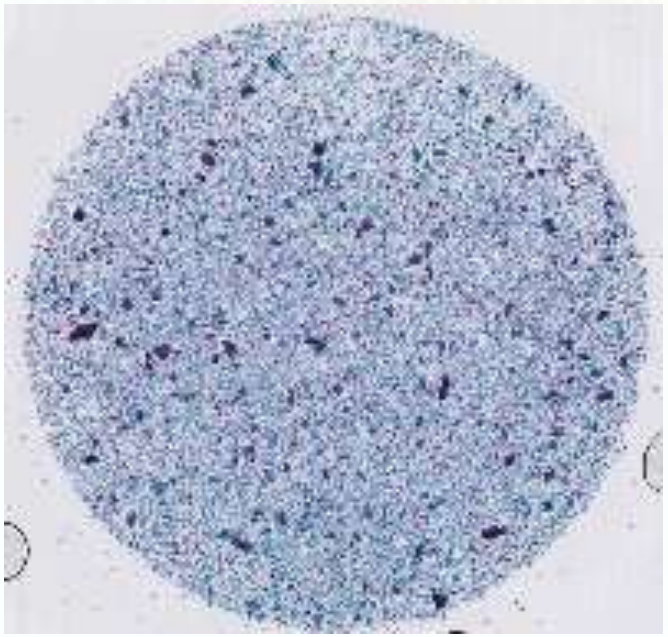
Virtual Fluorescence Slides



Z-axis scanning and virtual focus



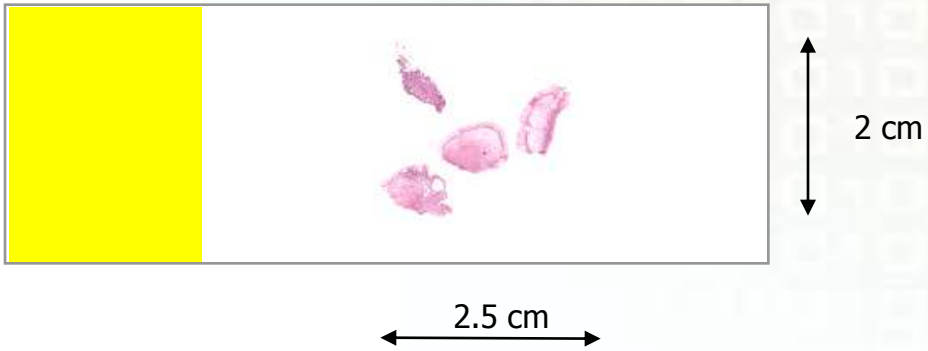
Cervical cytology



17 Gigabyte : TIFF JPEG compressed

25 slides = 1 Terabyte

These are large images !



At x40 objective magnification the required resolution is
0.24 microns per pixel = 104,000 x 85,000 linear pixels

25 Gigabytes

JPEG2000 compression 25:1

RVH Belfast: 300 cases a day > 100 Terabytes of data a year

Technical challenges

♦ Defining standards ♦

♦ Storage of Virtual Slides ♦

♦ Enhancing on-line delivery of gigapixel imagery ♦

♦ Tools for viewing and interacting with virtual slides ♦

♦ Algorithms for automated machine vision of gigapixel images ♦

♦ High performance computing for tissue imaging ♦

It’s not the virtual slide that counts – it’s what we do with it.

Application opportunities

Making virtual microscopy work

Education and Training

Quality Assurance

Tissue archiving

Tissue Research

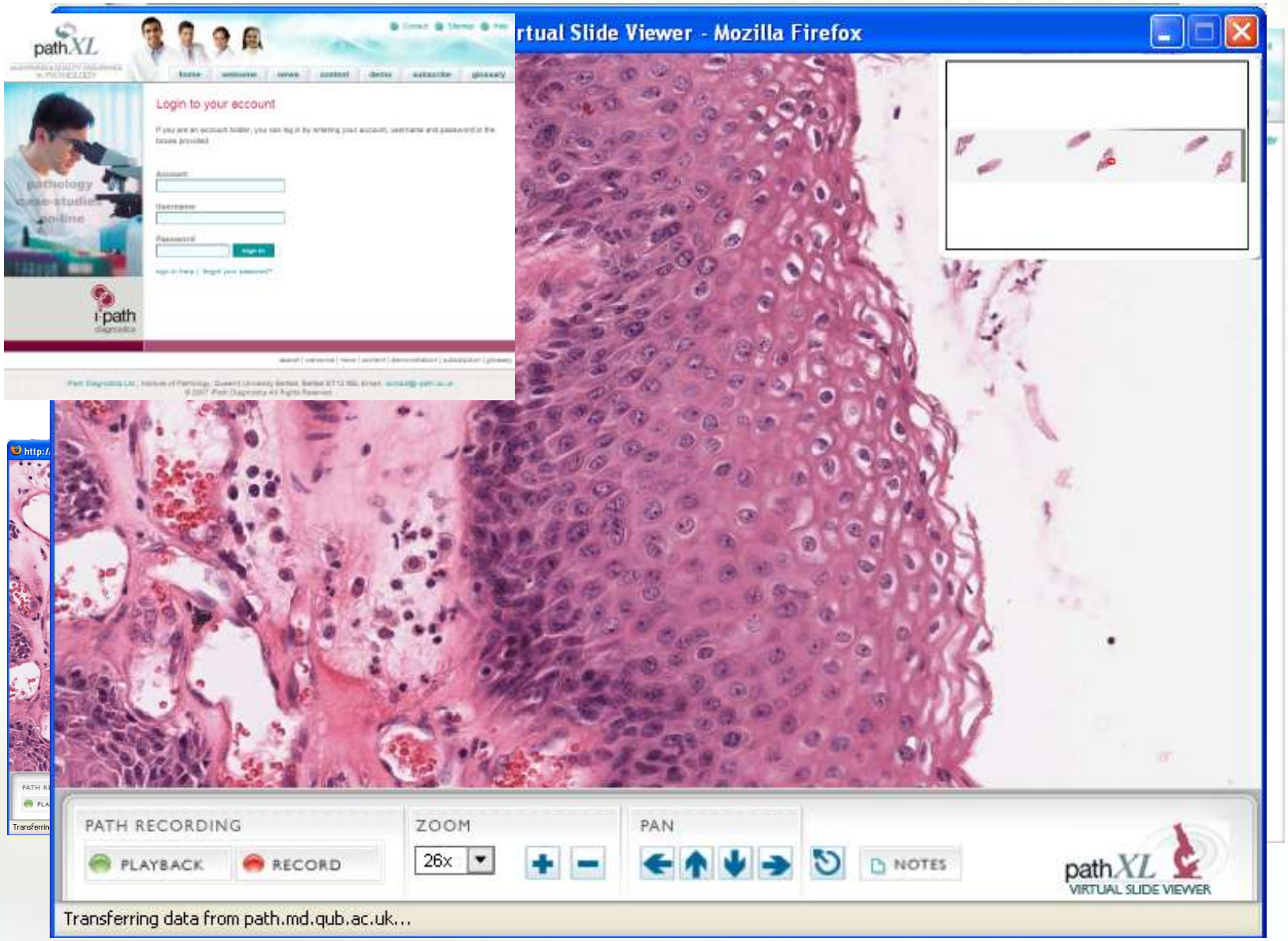
Queen's University Belfast

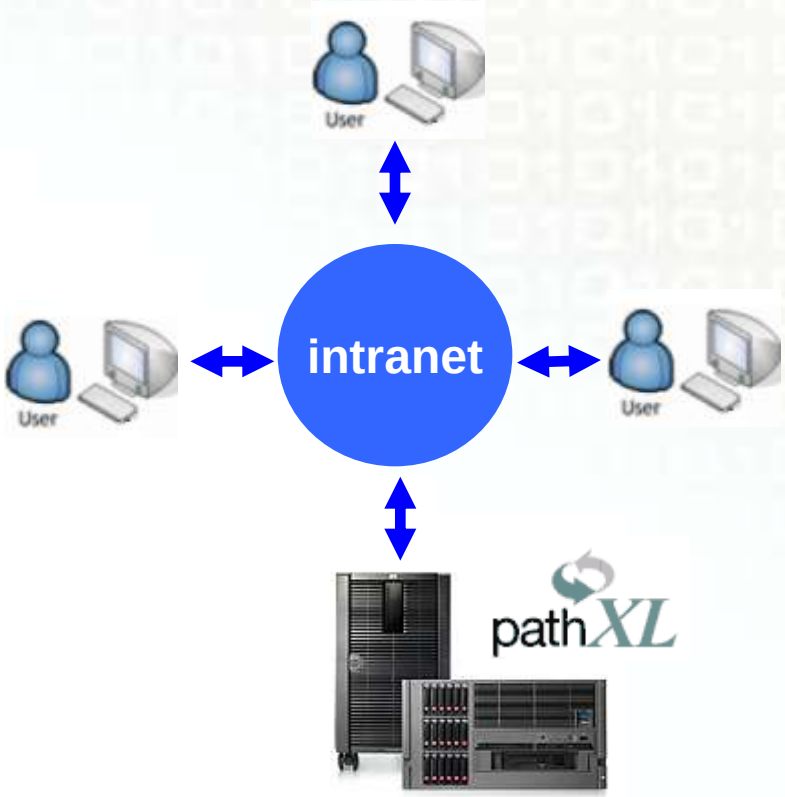
i·path diagnostics

PathXL®

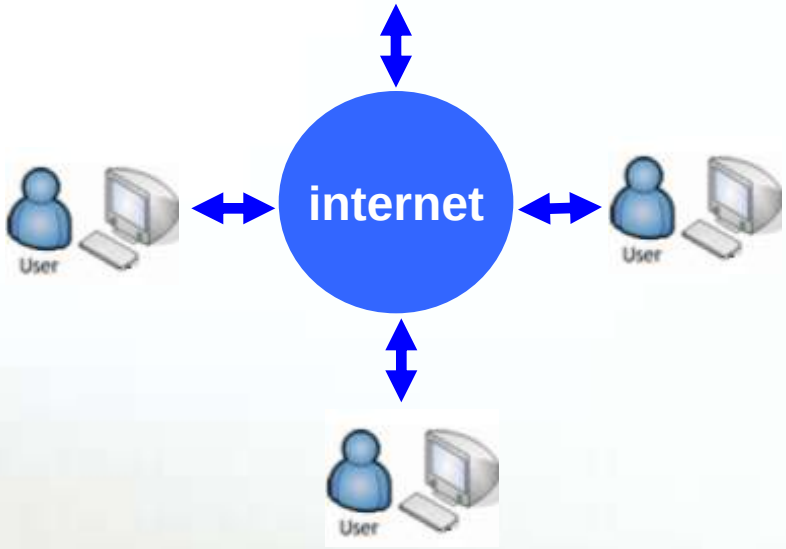
Making Virtual Microscopy happen

www.pathxl.com

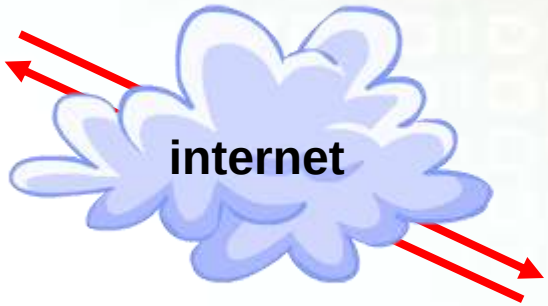




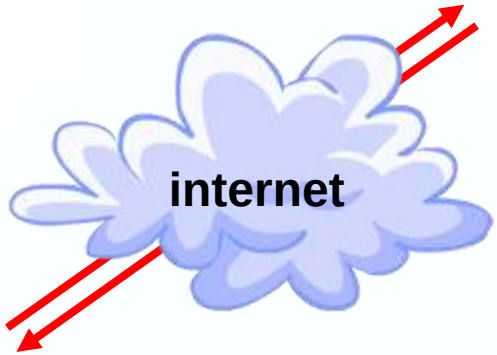
Virtual slide server



User/student/trainee/researcher

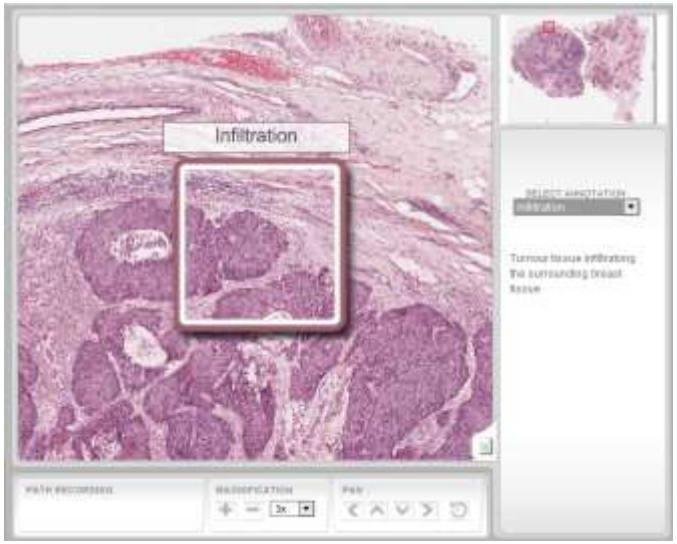


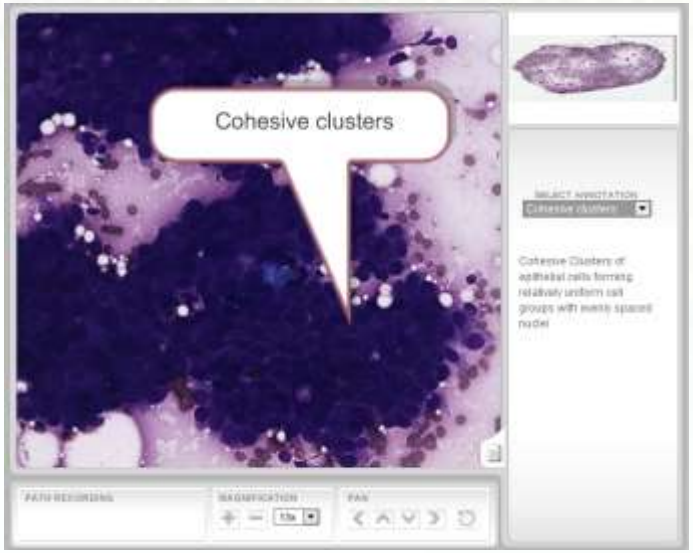
Virtual slide server



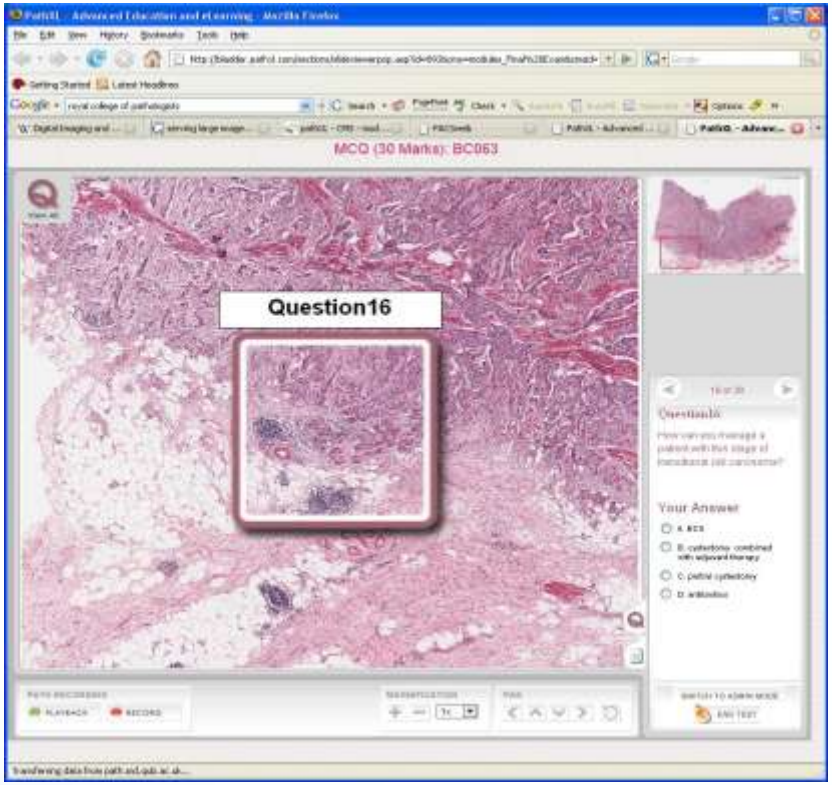
Author/Administrator

Slide Annotations for Training and Education





Virtual Slides for Examination and Proficiency Testing



Setting virtual slide questions on-line
Recording responses centrally on-line
Setting examinations on-line

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http://www.pathxl.com/sections/default.asp?secid=3_1&id=96&cms=modules_Breast%20Histopathology&cmsid=9_34

Getting Started Latest Headlines http://www.lucid-tec...

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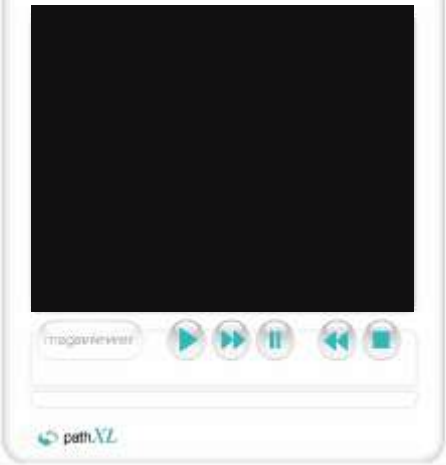
- Breast Cytopathology
- Cervical Histopathology
- Breast Histopathology
- Urine Cytopathology
- Cervical LBC
- UKNEQAS ICC
- Tissue Microarrays
- Melanocytic Skin Lesion Study
- MDT Meeting
- Lectures

you are here: home > modules > breast histopathology > case 9

Case 9

< previous case | next case >

Breast Histopathology Case 9



View in PathXL slide viewer

View in standard slide viewer

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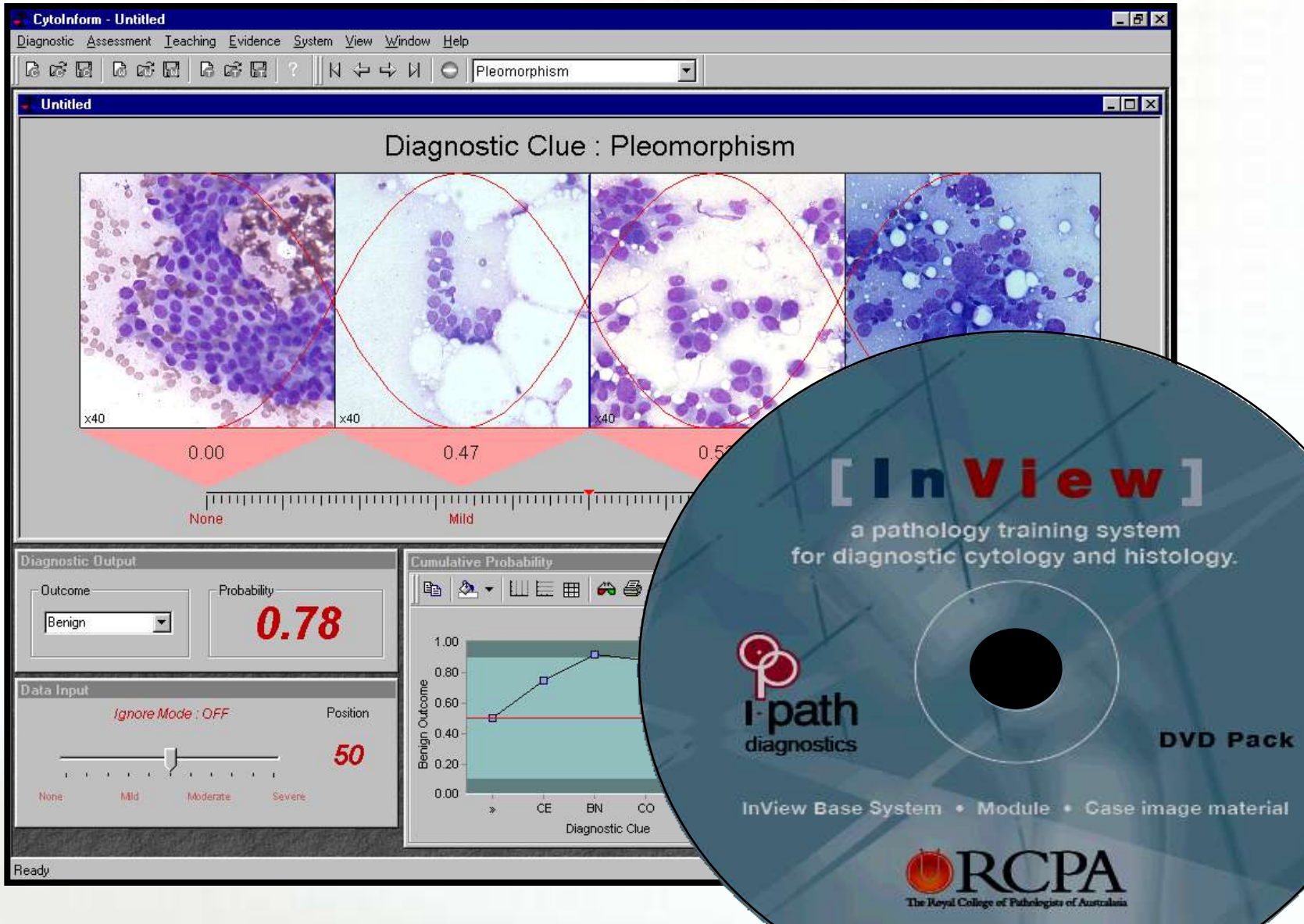
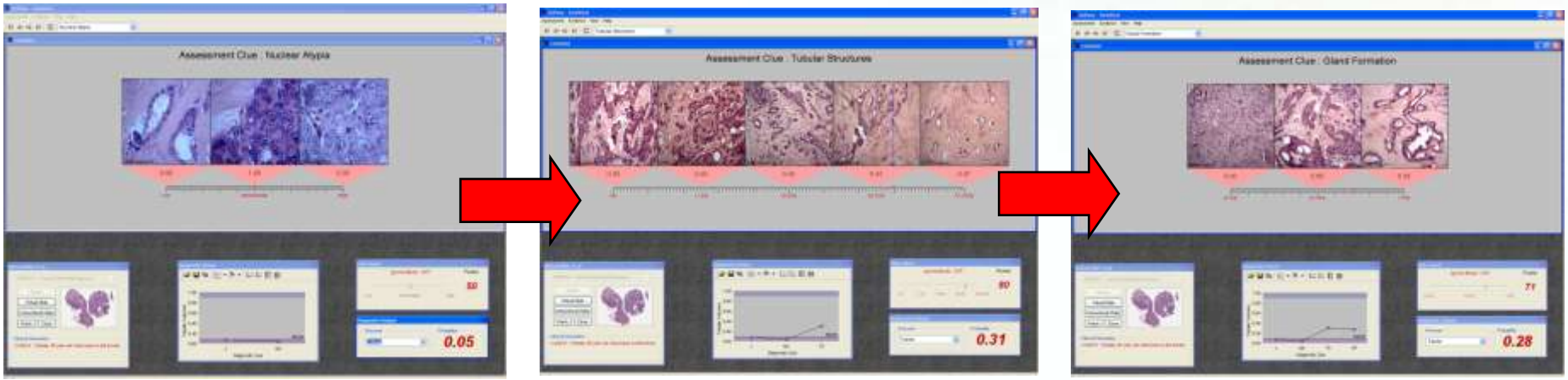
InView®

"Learning by diagnostic simulation"



Unique approach to training in pathology

Stepping through the diagnostic clues

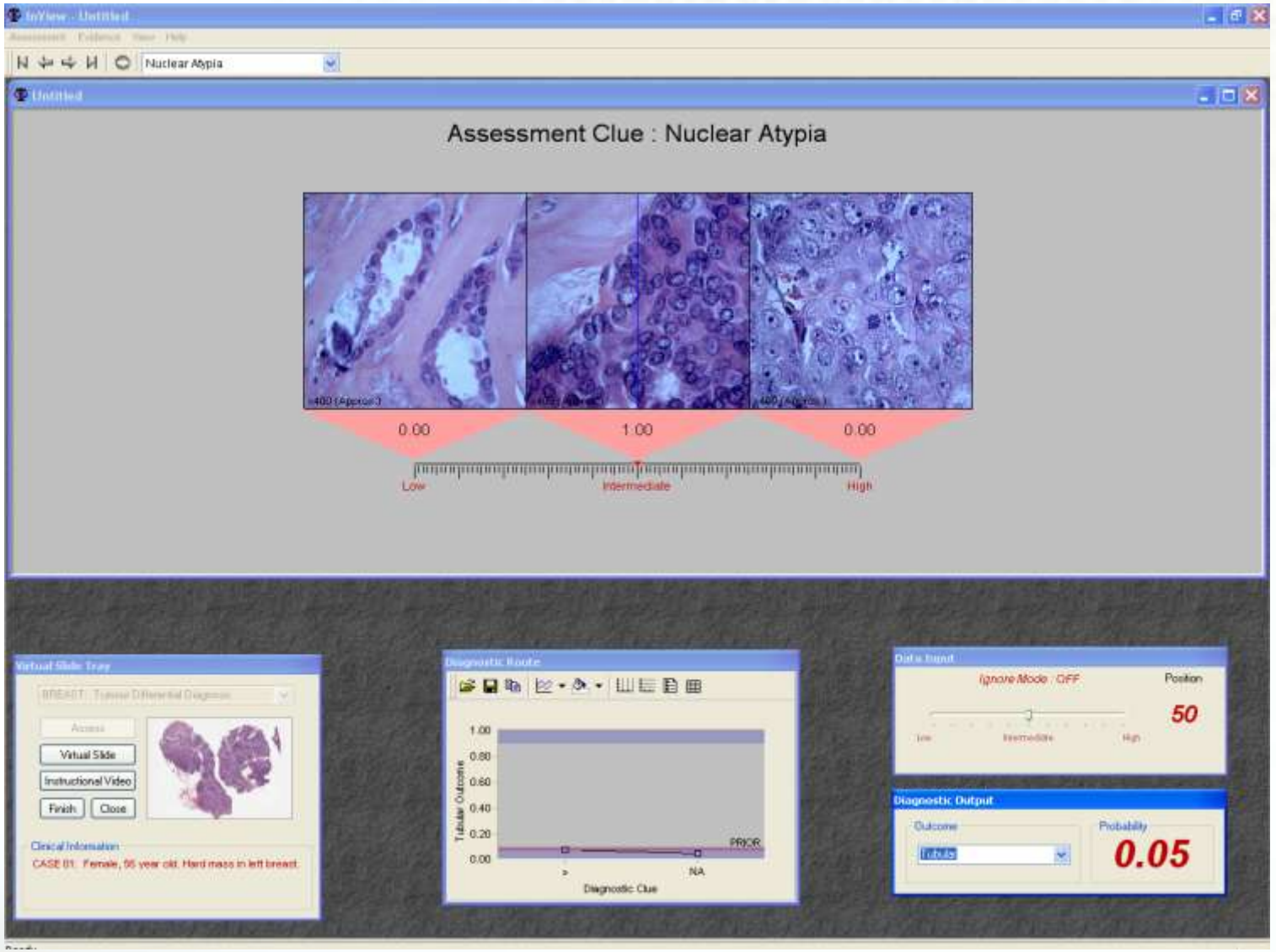


Visual comparison with template images

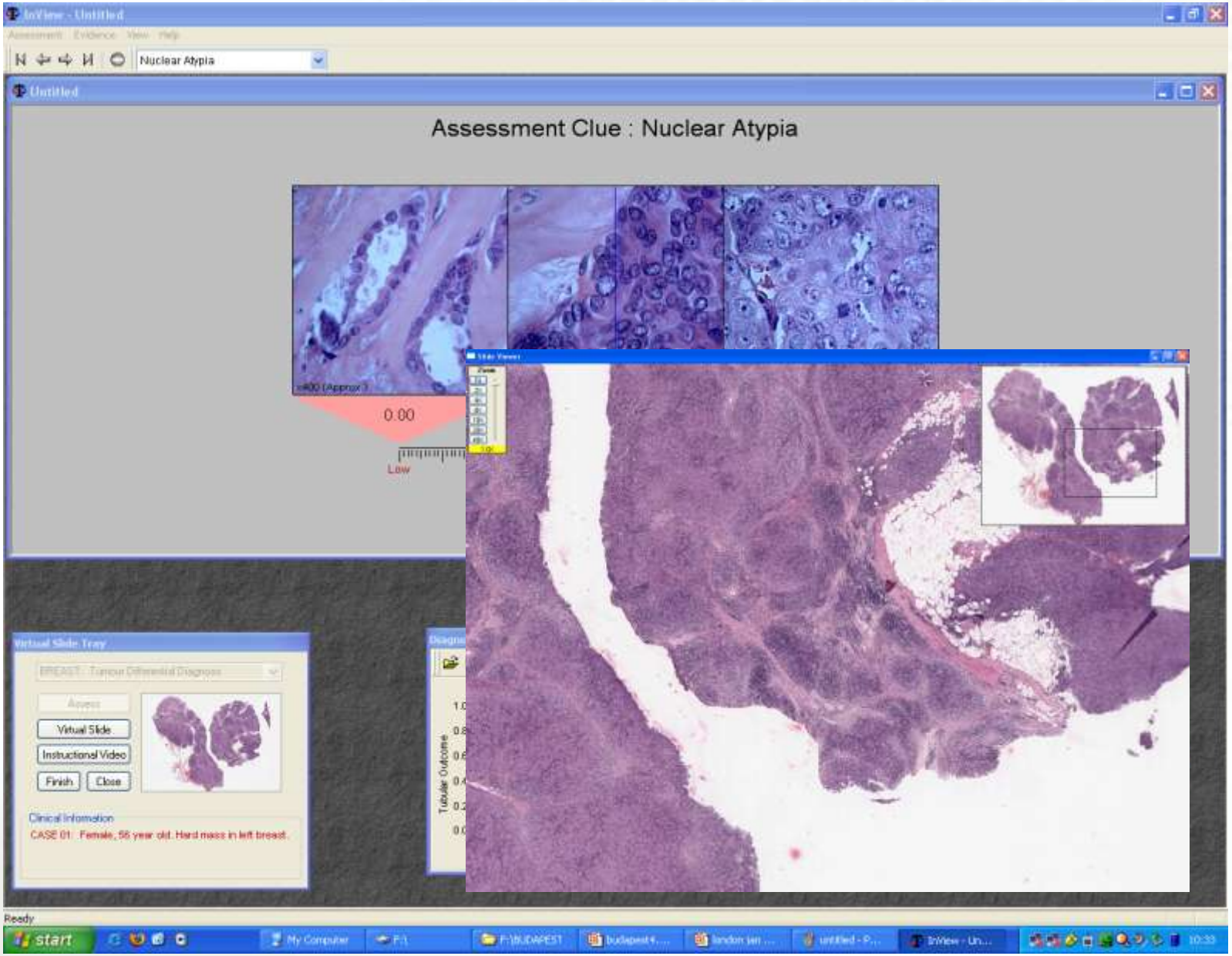
Diagnostic probability

Diagnostic map

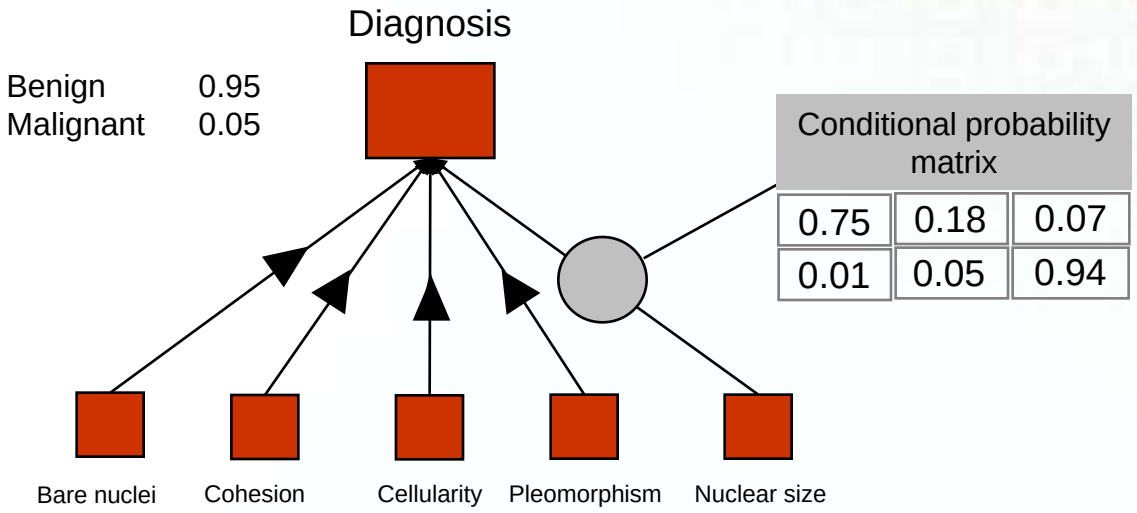
InView™



i·path diagnostics


Nuclear Atypia
Assessment Clue : Nuclear Atypia
0.00
Low
Virtual Slide Tray
Virtual Slide
Instructional Video
Finish
Close
Clinical Information
CASE 01: Female, 56 year old. Hard mass in left breast.
Tubular Outcome
Ready
start

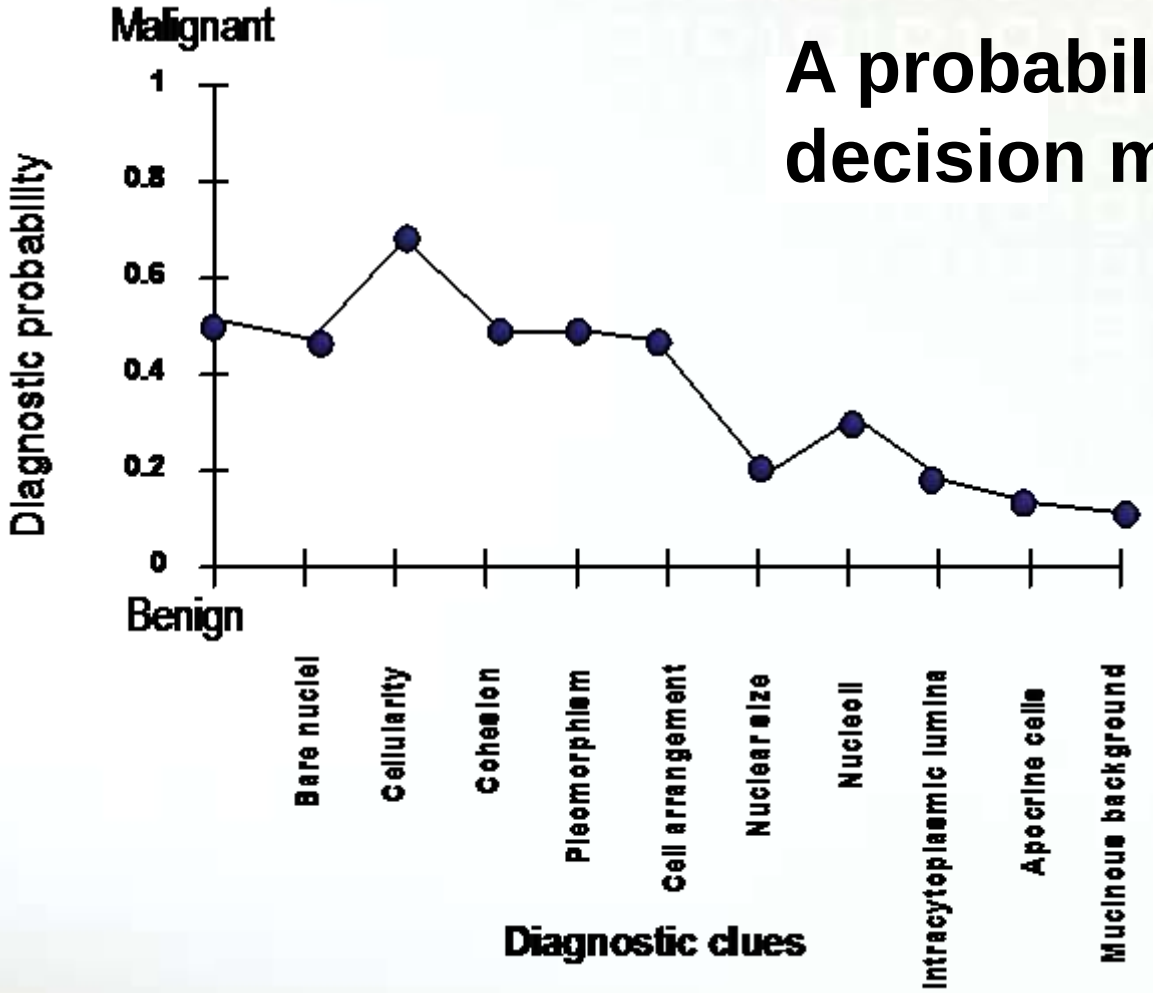
Bayesian belief network engine with fuzzy logic representation of language



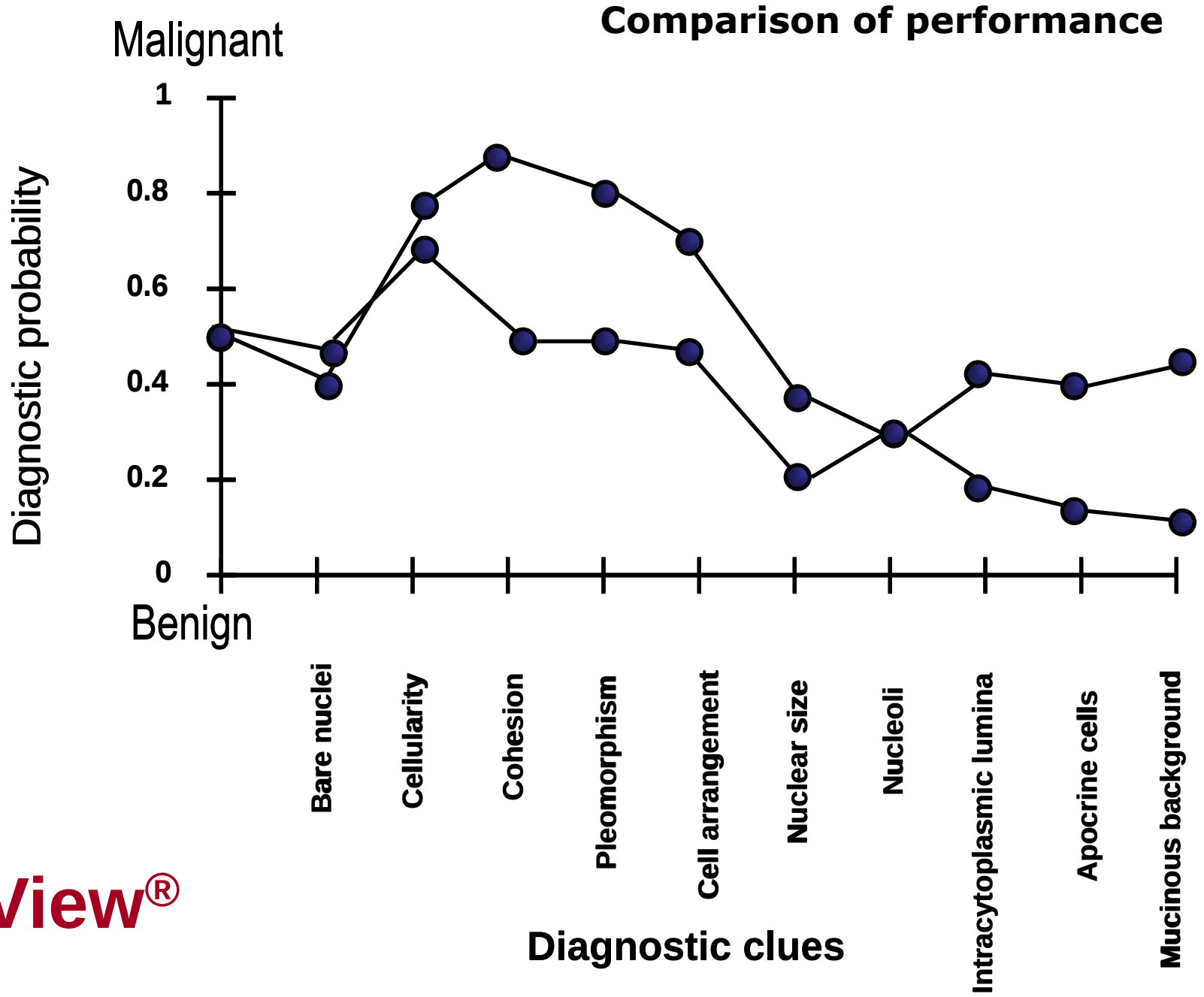
Allows us to model and record diagnostic knowledge from experts

i·path diagnostics

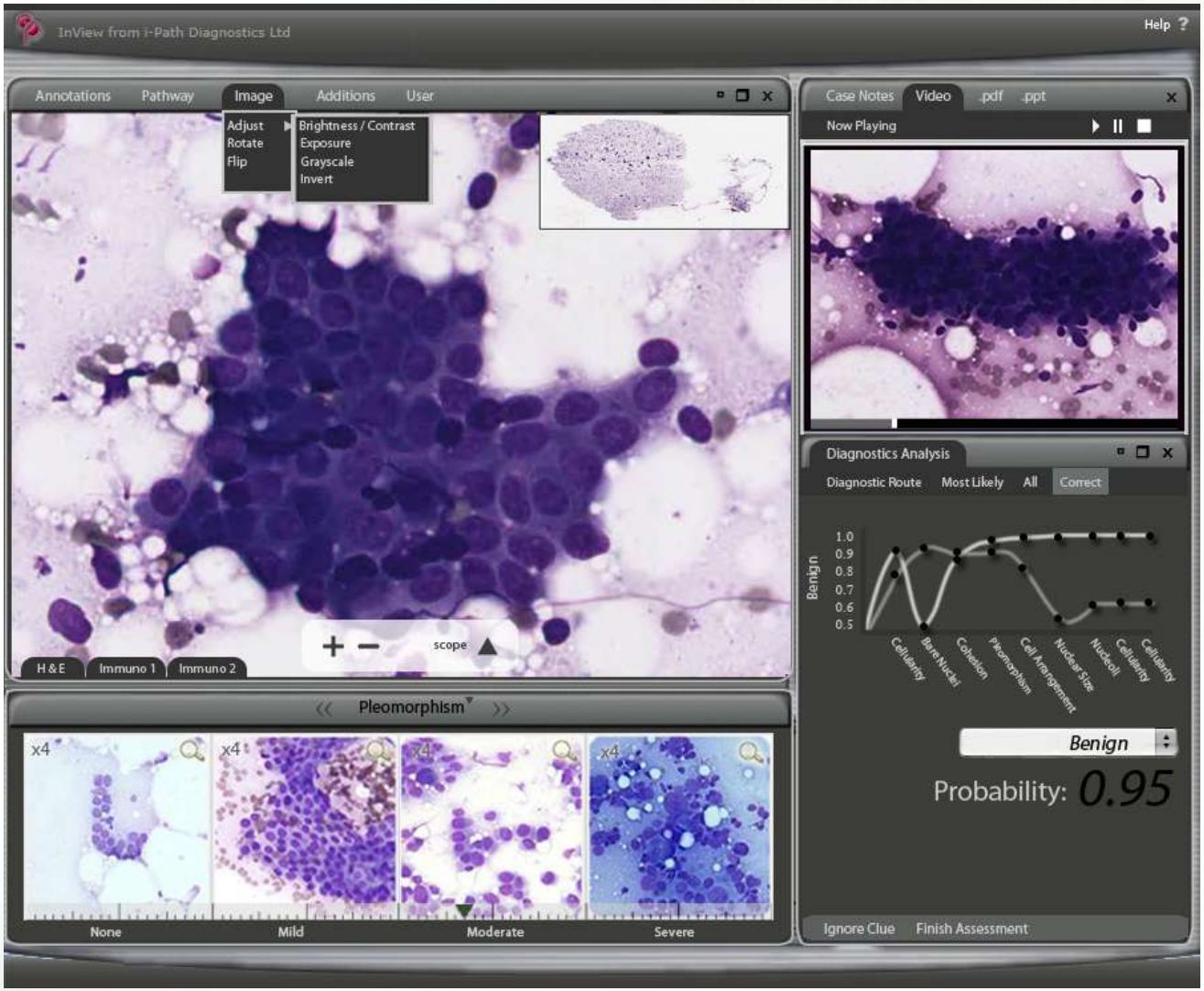
A probability decision map



i·path diagnostics


Comparison of performance
Malignant
1
0.8
0.6
0.4
0.2
0
Benign
Diagnostic probability
Bare nuclei
Cellularity
Cohesion
Pleomorphism
Cell arrangement
Nuclear size
Nucleoli
Intracytoplasmic lumina
Apocrine cells
Mucinous background
Diagnostic clues

InView®


InView from i-Path Diagnostics Ltd
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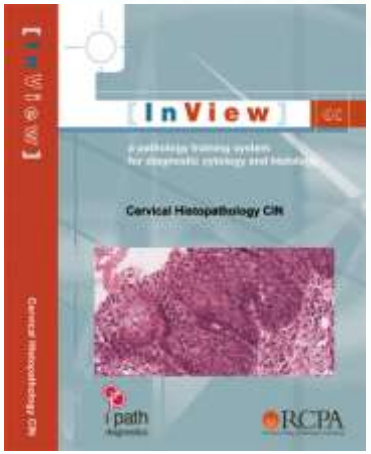
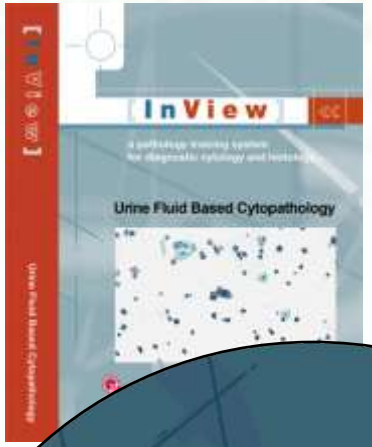
Flip
Brightness / Contrast
Exposure
Grayscale
Invert
scope
H & E
Immuno 1
Immuno 2
Case Notes
Video
.pdf
.ppt
Now Playing
Diagnostics Analysis
Diagnostic Route
Most Likely
All
Correct
Benign
1.0
0.9
0.8
0.7
0.6
0.5
Cellularity
Bare Nuclei
Cohesion
Pleomorphism
Cell Arrangement
Nuclear Size
Nucleoli
Cellularity
Cellularity
Benign
Probability: 0.95
Ignore Clue
Finish Assessment
Pleomorphism
x4
None
Mild
Moderate
Severe

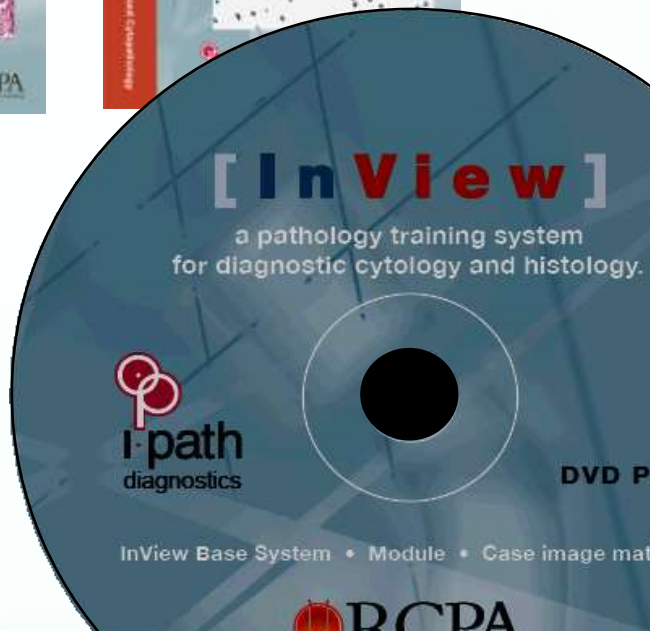
InView®

"Learning by diagnostic simulation"





Endometrial Neoplasia
Grading in Prostate Cancer
Soft Tissue Tumours
Salivary Gland Tumours
Melanocytic Skin Lesions



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Changing the face of digital pathology

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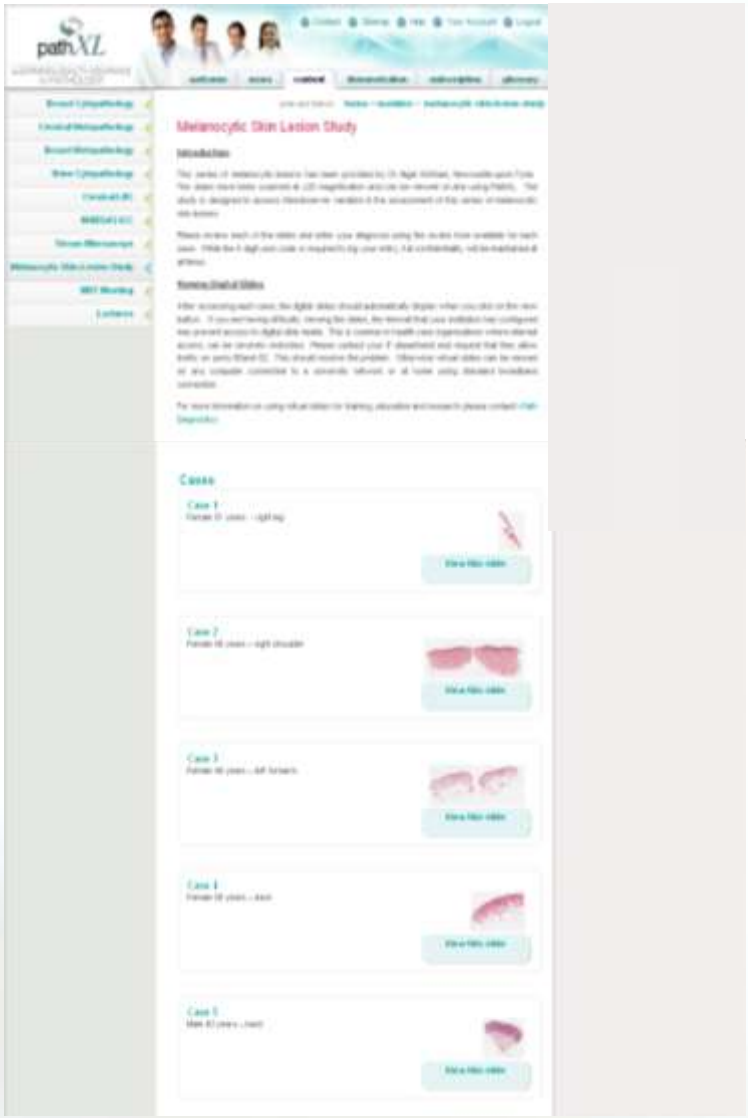
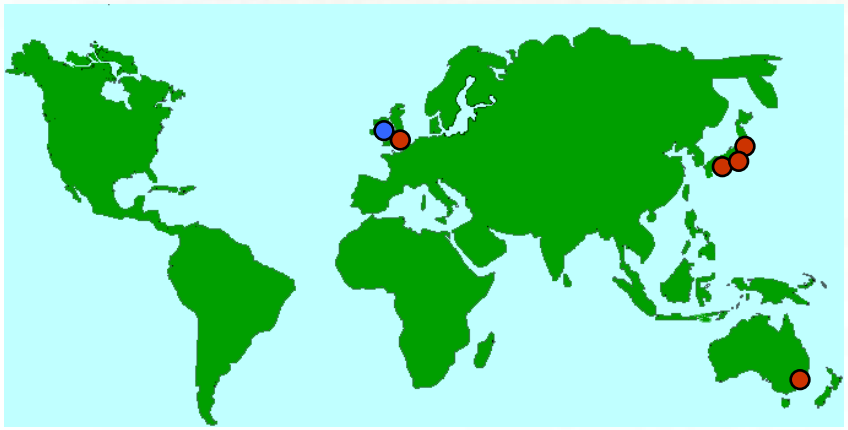
Virtual EQA

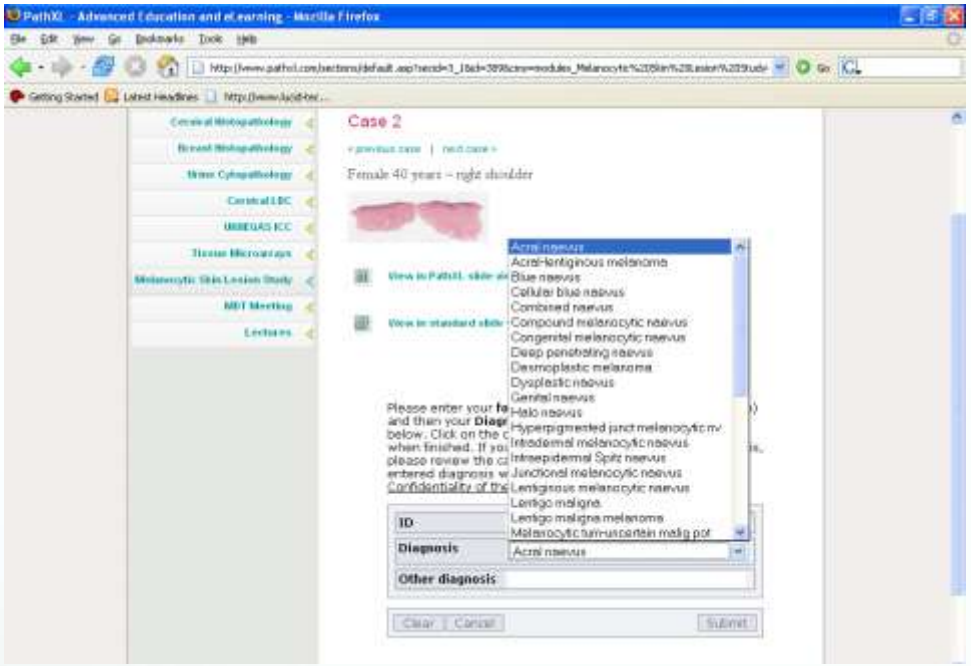
External Quality Control and Proficiency Testing

Virtual Slides for EQA

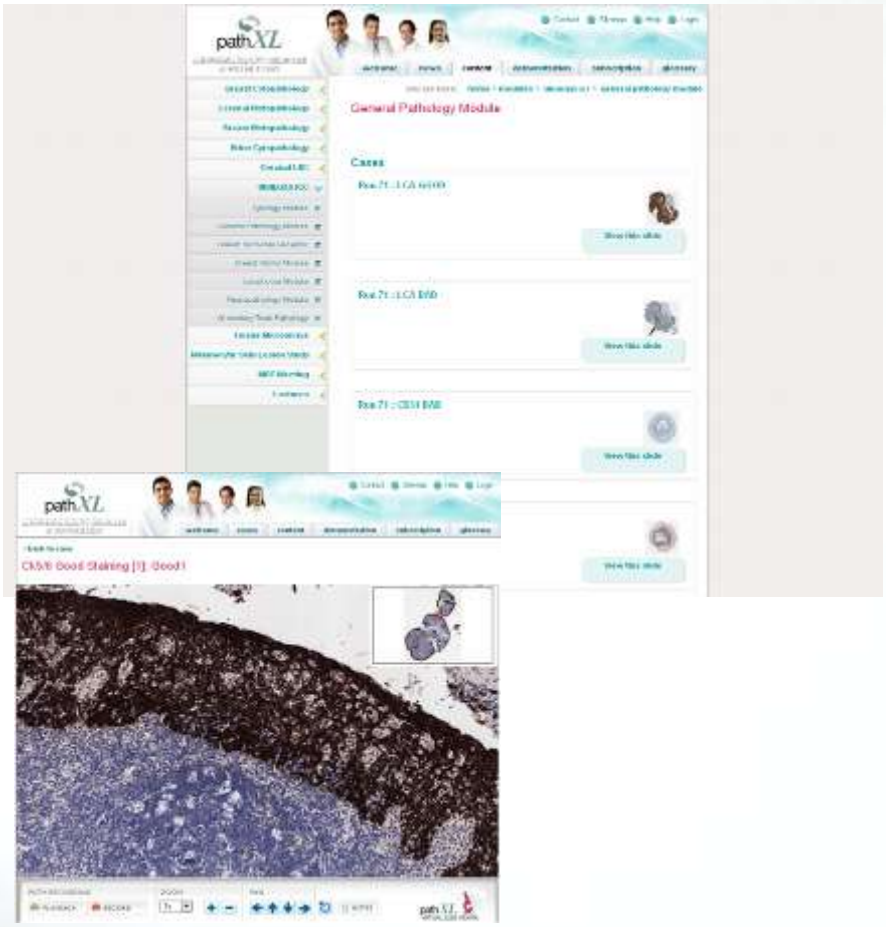
Melanocytic Skin Lesion Diagnosis in UK and Japan

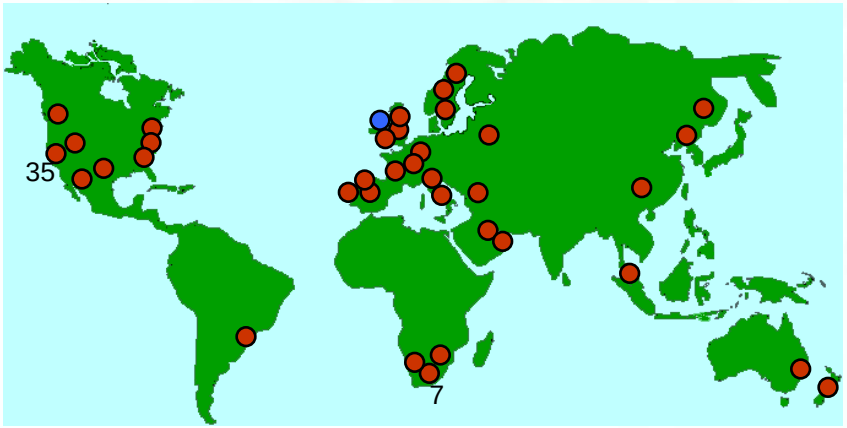






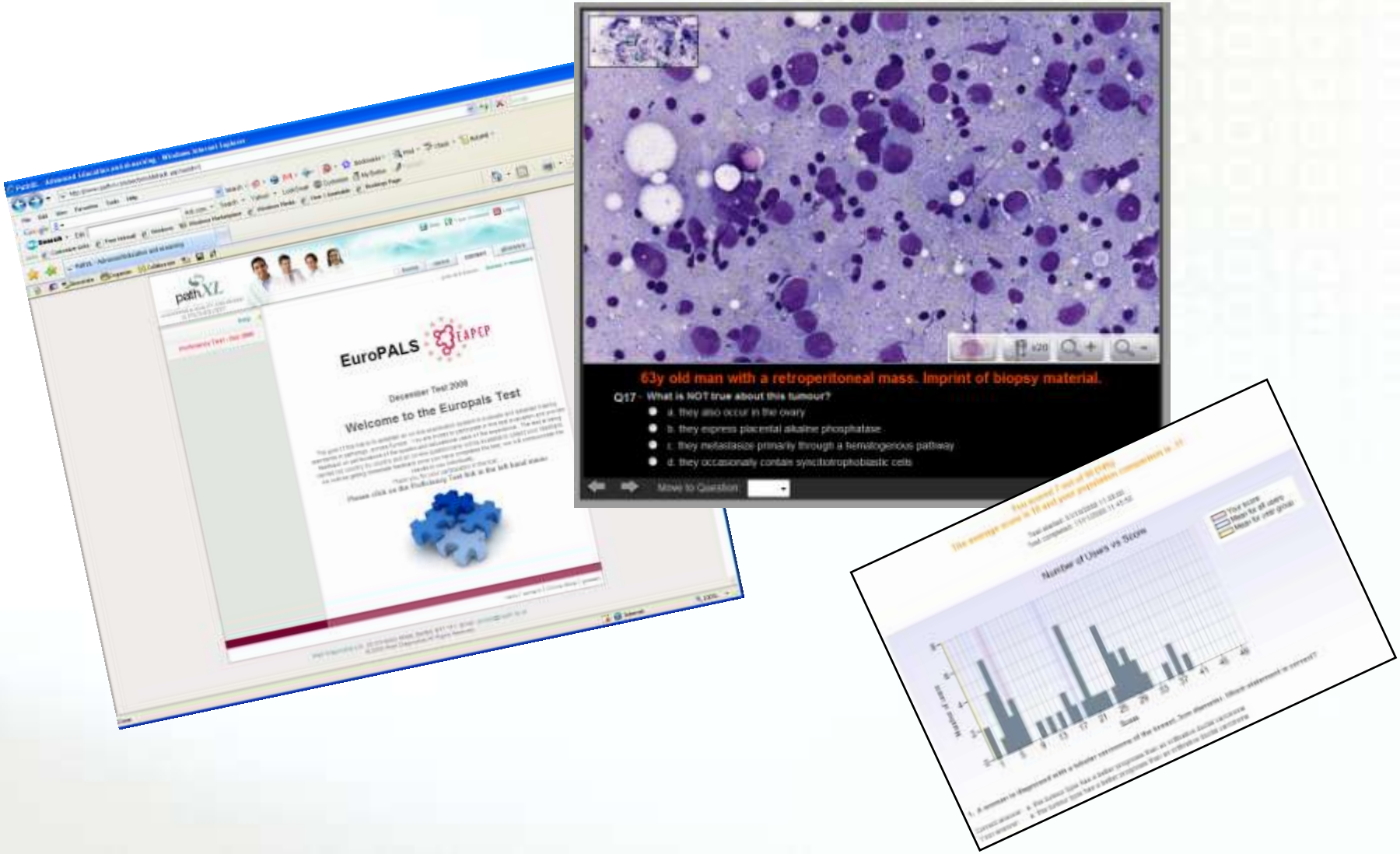
UKNEQAS IHC Programme





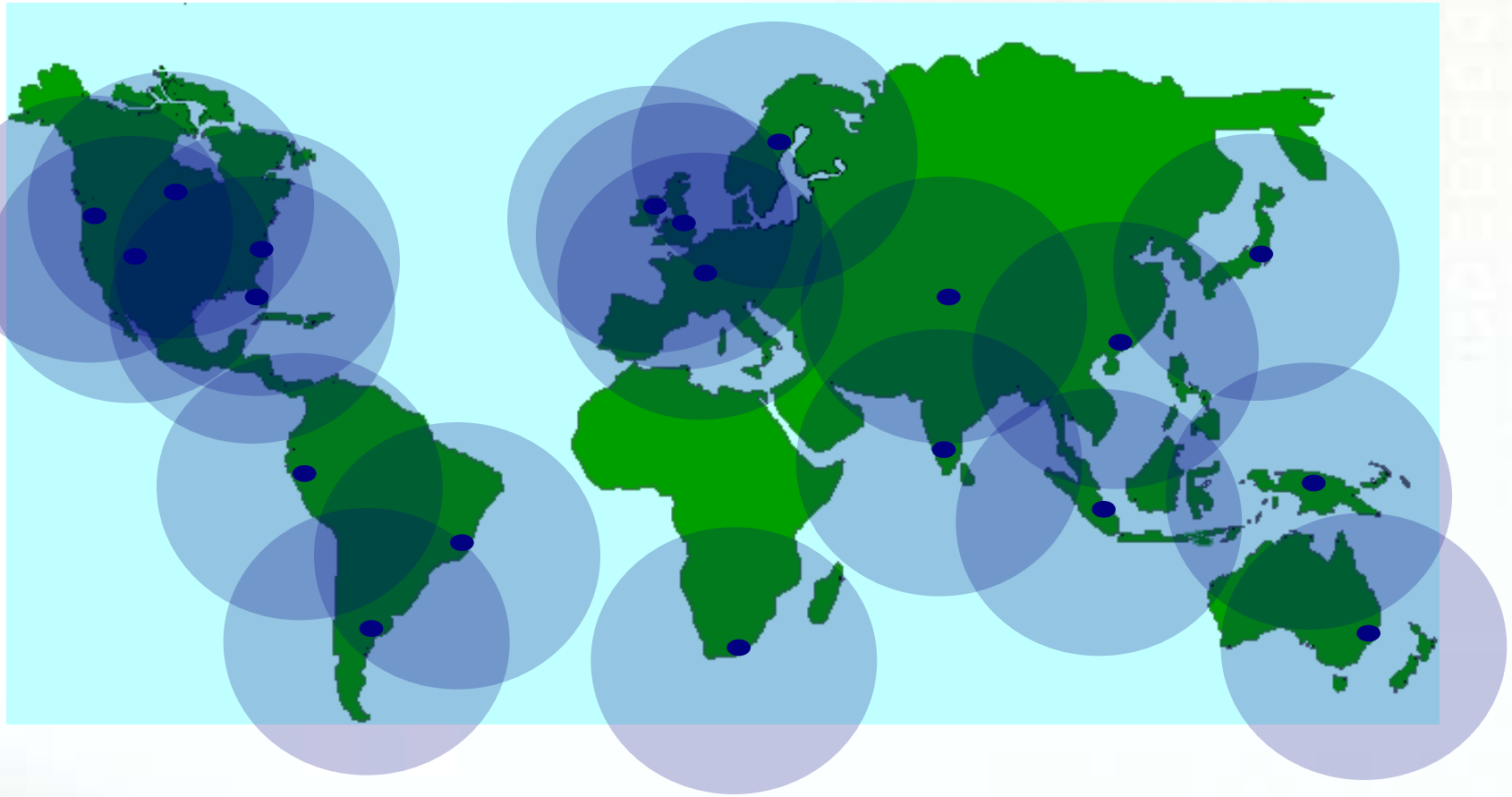
The need for worldwide VM service network of data centers with rapid access to image data globally

Proficiency Testing



i·path
diagnostics

hp
invent



Worldwide server architecture for delivery of high resolution imagery

Virtual Tissue Banking

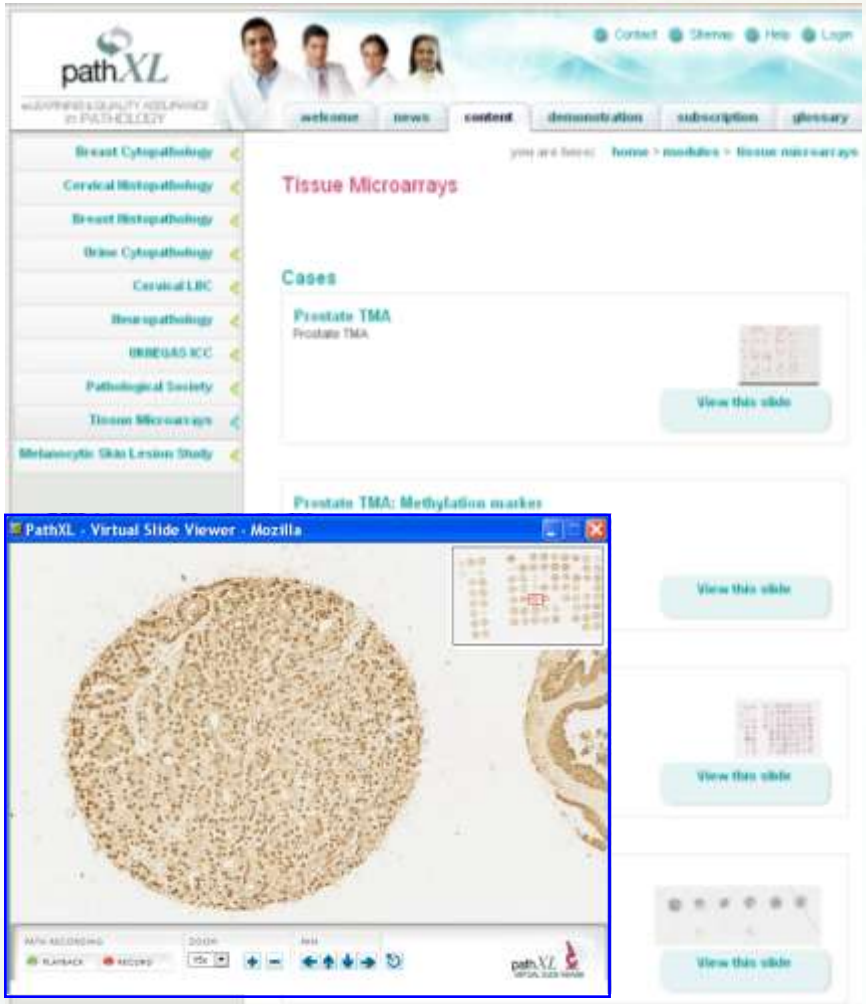
Confederation of Cancer Biobanks

OBBR Office of Biorepositories and Biospecimen Research

Glasgow Biobank
onCore UK
Tayside Tissue Bank
Wales Cancer Bank
Northern Ireland Tissue Bank

Northern Ireland Virtual Tissue Bank (NIVTA)
Bioimaging CTU, QUB

cancergrid



Queen's University Belfast

hp invent

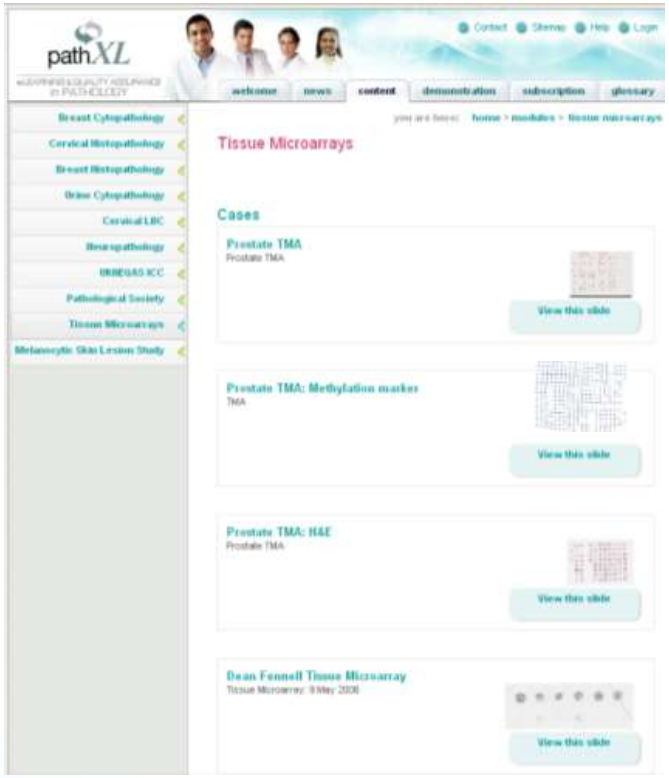
r&d office

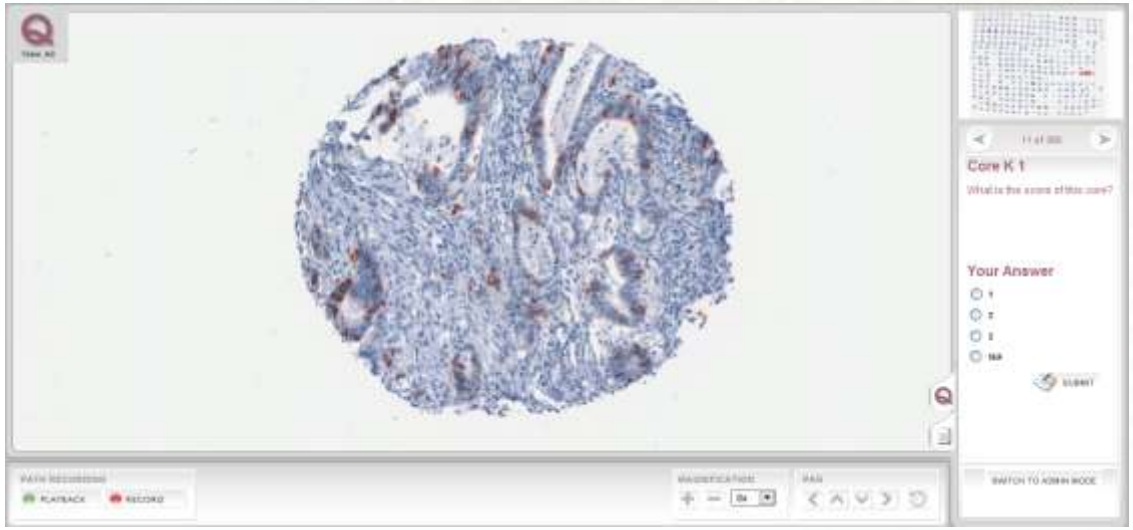
i·path diagnostics

Virtual slides for Tissue Archiving and Research

On-line scoring of TMAs and tissue samples

Enhancing biomarker evaluation





Leeds University (Gastric TMAs)
Cambridge University (Bladder BOXIT trial)
Queen's University (Mesothelioma)
Queen's University (Prostate response TMA)
Fusion Antibodies Ltd

Controlled vocabularies
Compatability with Data Exchange Standards
(Berman et 2003, CaBIG, CancerGrid, Dublin Core Header

Virtual slides for Tissue Archiving and Research

On-line evaluation of TMA

TMA generation

TMA context mapping

After

Before

Shortfalls in visual interpretation

Making the diagnosis **Scoring the biomarker**

Subjective criteria

Language – associated with uncertainty

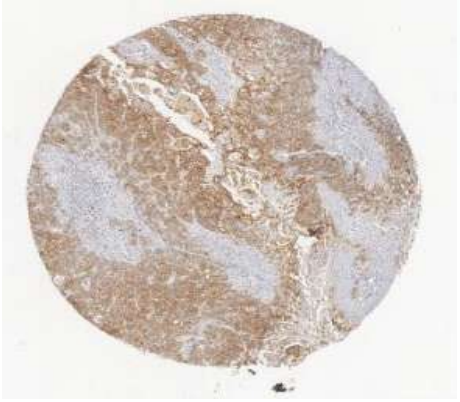
Disease “patterns” are based on predefined mind sets

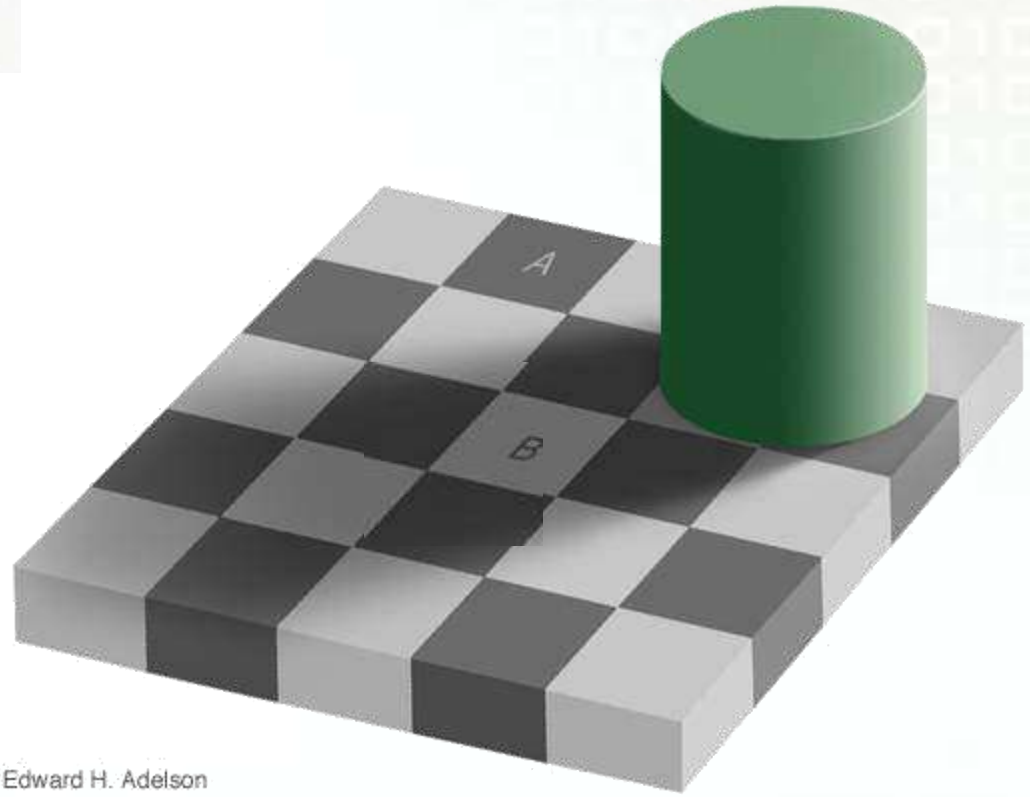
Not good at detecting quantitative differences

Open to interpretation

Poor reproducibility

Inaccuracy





Edward H. Adelson

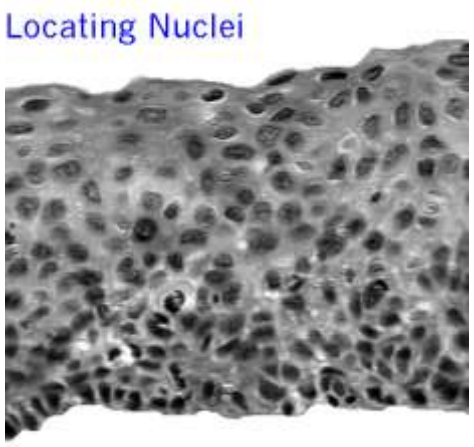
Disagreement in pathological diagnosis

	Kappa
Pre-invasive lesions of the bronchus (Nicholson – Histopathology 2001;38:202-208)	**0.55**
Cervical cytology *(Stoler – JAMA 2001;285:1500-1505)*	**0.46**
Cervical Histology *(McCluggage – Br J Obs Gynae 1998;105:206-210)*	**0.15 – 0.62**
Prostate Cancer *(Egevad – Urology 2001;57:291-295)*	**0.58**
Oral Dysplasia *(Warnakulasuriya – J Pathol 2001;194:294-297)*	**0.27 – 0.45**

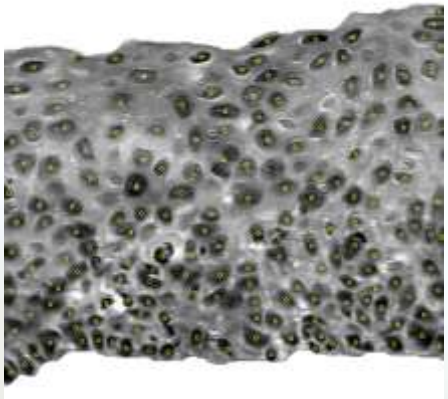
Variation in interpretation of renal transplant biopsies	**Furness et al. 2001**
Aberrant diagnoses by surgical pathologists	**Wakely 1998**
Dysplasia classification: pathology in disgrace	**Bosman. 2001**
“Individuality” in the specialty of surgical pathology	**Ackerman 2001**

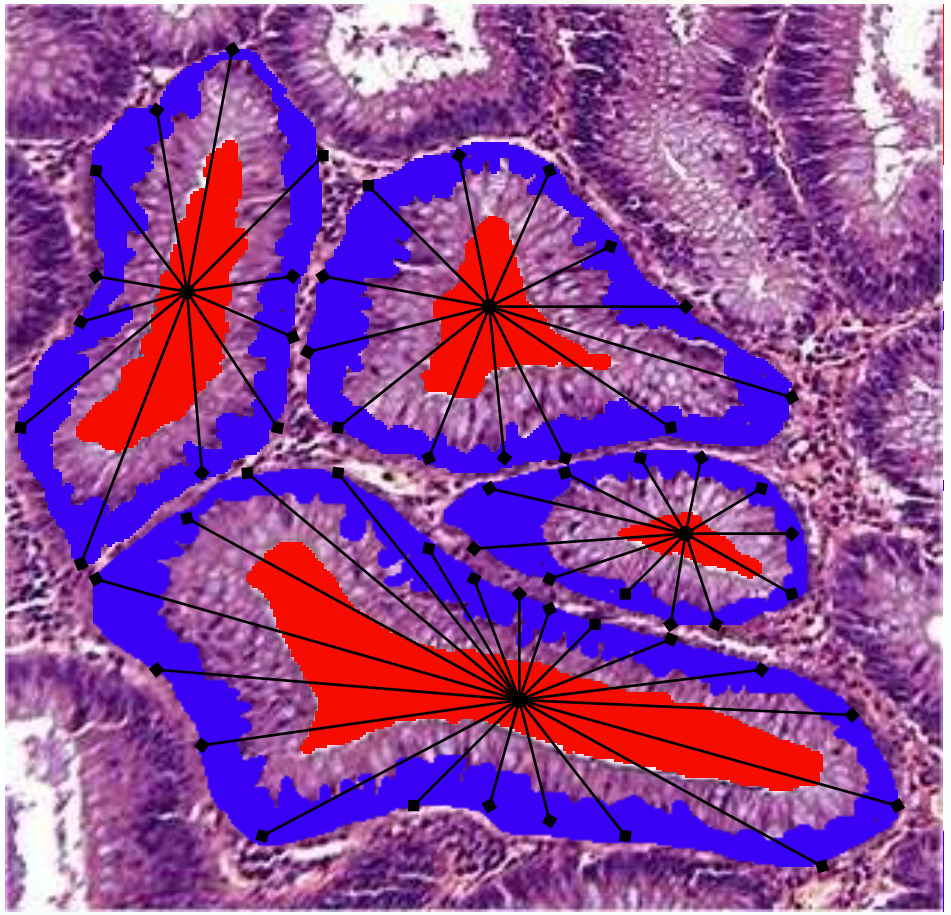
Enormous opportunities to explore improved methods of tissue diagnostics that are objective, reproducible and reliable

Image analytics Machine vision Quantitative evaluation Tissue classification

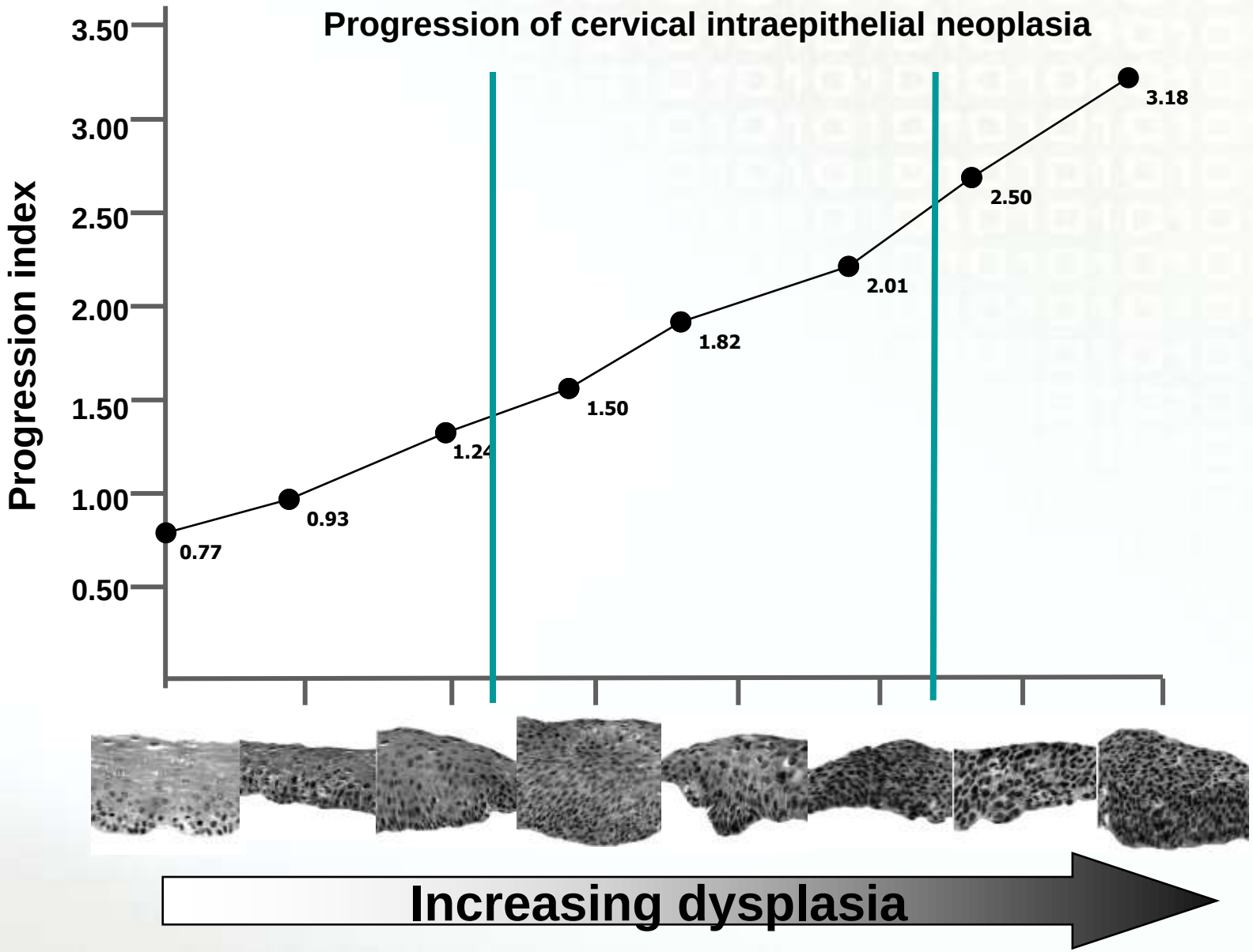


Cervical preneoplasia





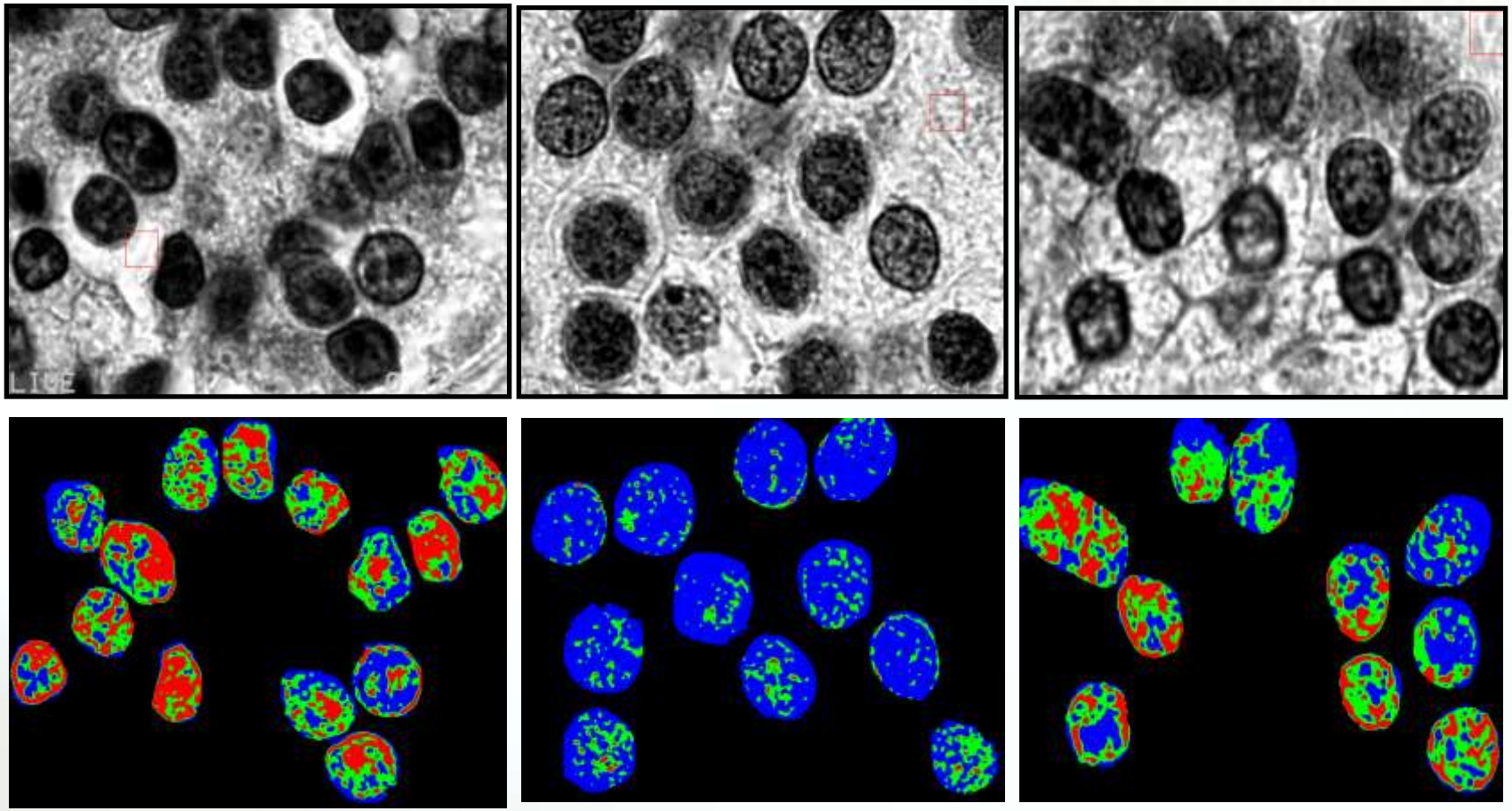
Colorectal adenomas


Progression of cervical intraepithelial neoplasia
Progression index
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.77
0.93
1.24
1.50
1.82
2.01
2.50
3.18
Increasing dysplasia

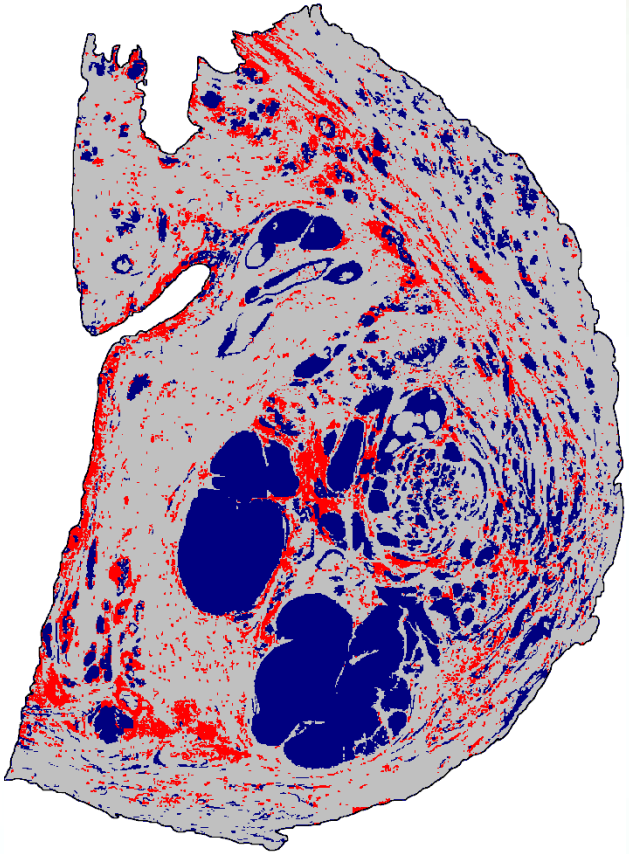
Augmented Visualisation in Pathology

Prostatic neoplasia

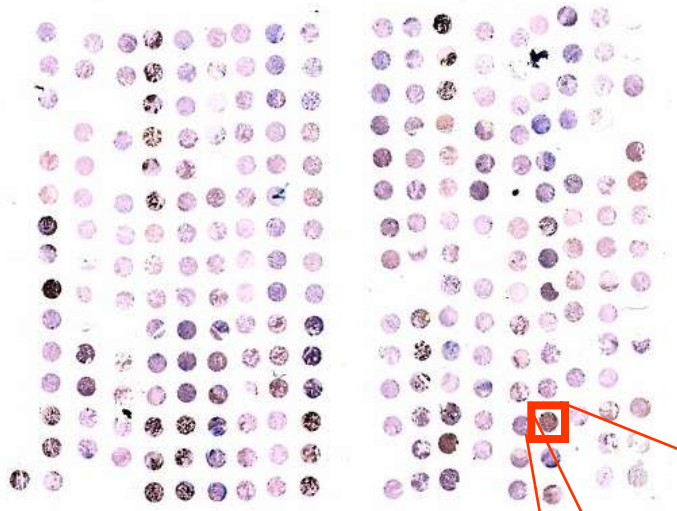
BPH | PIN | Prostate Cancer

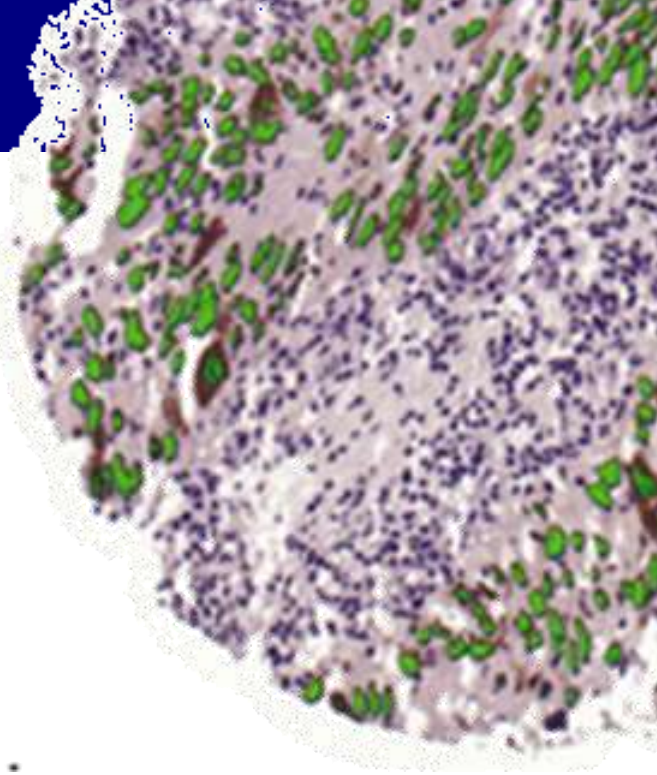


Machine vision on virtual slides

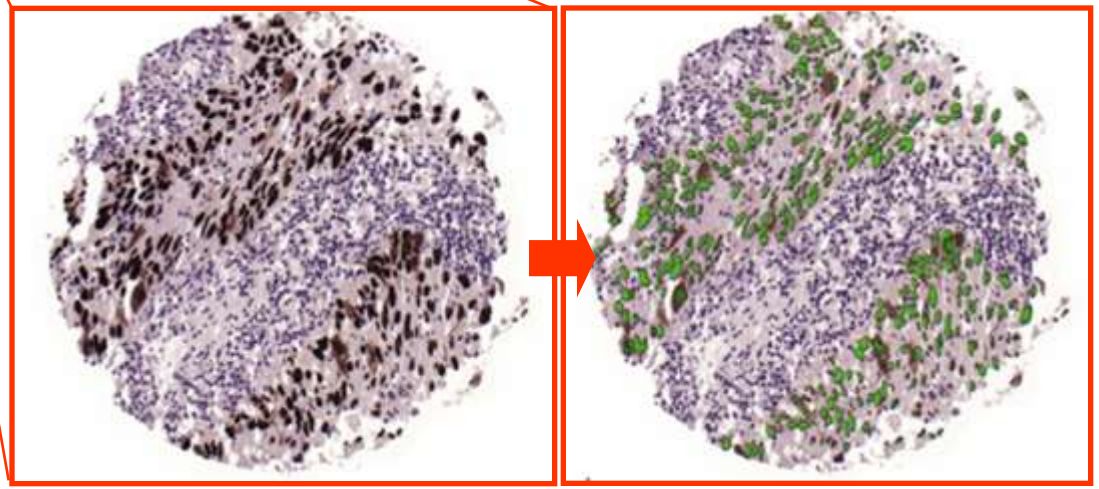


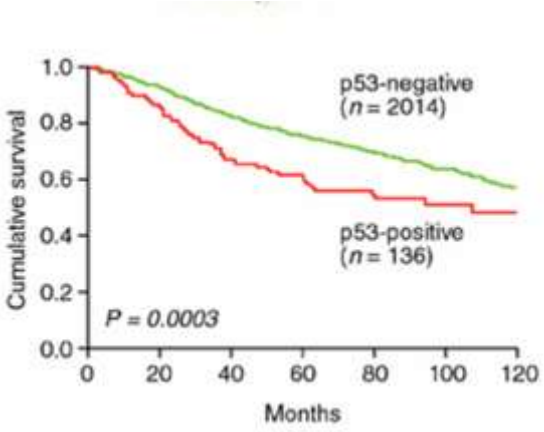
Computer vision analysis of Tissue Microarrays





IOD=1.75 = Score 3



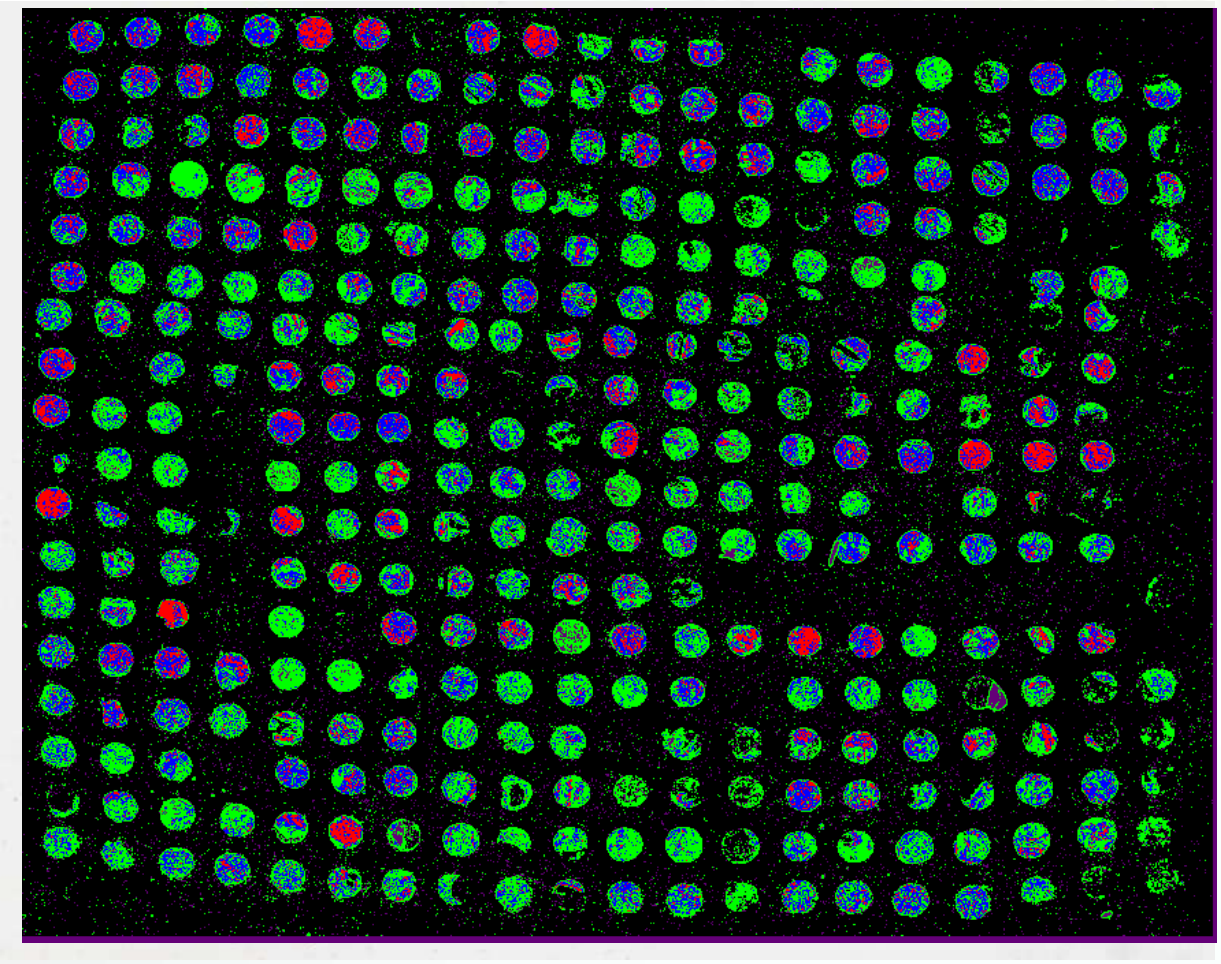


High Performance Computing (HPC) using Clusters

Significant speed enhancements for densitometric analysis of gastric TMA

David McCleary

Augmented Visualisation in TMA assessment



High Throughput Analysis of TMAs

Speeding analysis

Providing objectivity and reproducibility

For algorithm development and evaluation

For pre-selection of markers for manual analysis

For more sensitive scoring of markers for clinical evaluation

Multiresolution texture analysis, CBIR and CBR

TABLE I
Texture Feature Descriptions

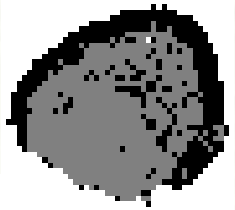
Texture feature	Expression
Average intensity	$m = \sum_{i=0}^{L-1} z_i p(z_i)$
Average contrast	$\sigma = \sqrt{\mu_2(z)}$
Smoothness	$R = 1 - 1/(1+\sigma^2)$
3rd Moment	$\mu_3 = \sum_{i=0}^{L-1} (z_i - m)^3 p(z_i)$
Uniformity	$U = \sum_{i=0}^{L-1} p^2(z_i)$
Entropy	$e = -\sum_{i=0}^{L-1} p(z_i) \log_2 p(z_i)$
Contrast	$F_{Con}^{Har} = \sum_{i,j} \lvert i-j \rvert^2 p(i,j)$
Correlation	$F_{Cor}^{Har} = \sum_{i,j} \frac{(i-\mu_i)(j-\mu_j)p(i,j)}{\sigma_i \sigma_j}$
Angular second moment	$F_{ASM}^{Har} = \sum_{i,j} p^2(i,j)$
Inverse difference moment	$F_{IDM}^{Har} = \sum_{i,j} \frac{p(i,j)}{1+\lvert i-j \rvert}$

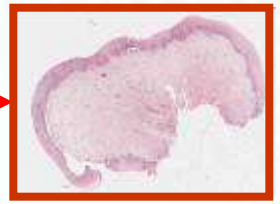
Where z_i is a random variable indicating intensity, $p(z)$ is the histogram of the intensity level in a region, L is the number of possible intensity levels, $\mu_2(z)$ is the variance, $p(i,j)$ is GLCM, $\mu_i = \sum_{i,j=0}^{N-1} i(p(i,j))$ and $\mu_j = \sum_{i,j=0}^{N-1} j(p(i,j))$ are GLCM means, whereas $\sigma_i = \sqrt{\sum_{i,j=0}^{N-1} p(i,j)(i-\mu_i)^2}$ and $\sigma_j = \sqrt{\sum_{i,j=0}^{N-1} p(i,j)(j-\mu_j)^2}$ are GLCM STD.

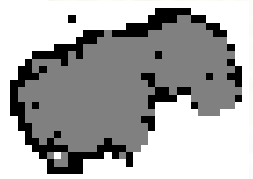
Test case

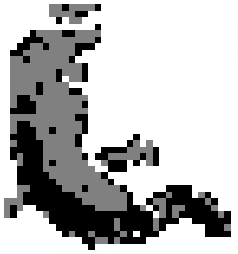
Similarity metric
(Hamming Distance)

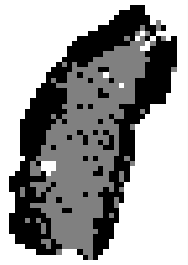
Tissue archive











Case-based reasoning

Growing numbers of virtual tissue archives

Storage and Search?

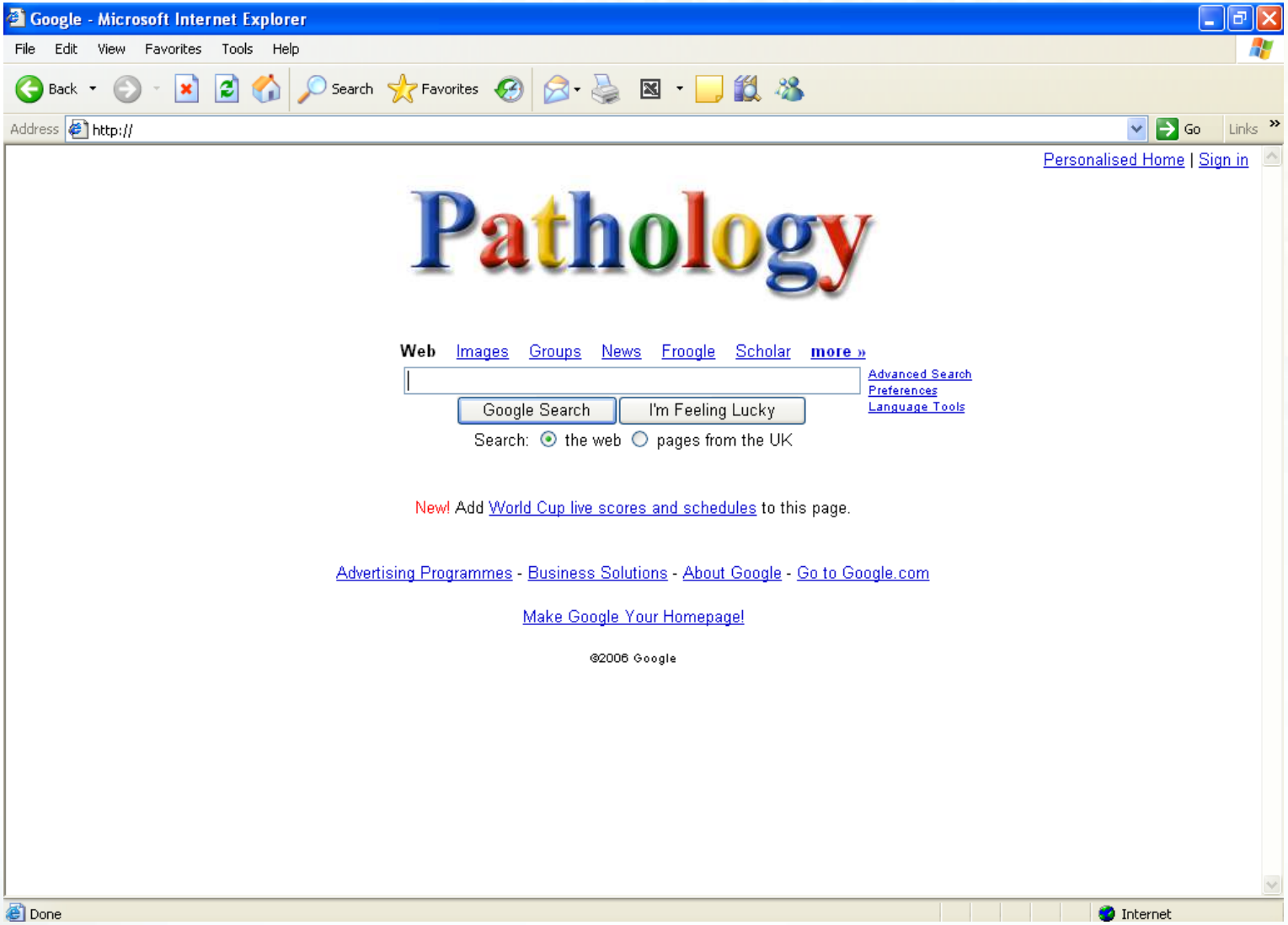


Image Search and content-based image retrieval

Acknowledgements

Jim Diamond

David McCleary
Andrena McCavigan
Yin Hai Li

Sid Trewin
Alan Lyons
Adam Askew
Stewart Church