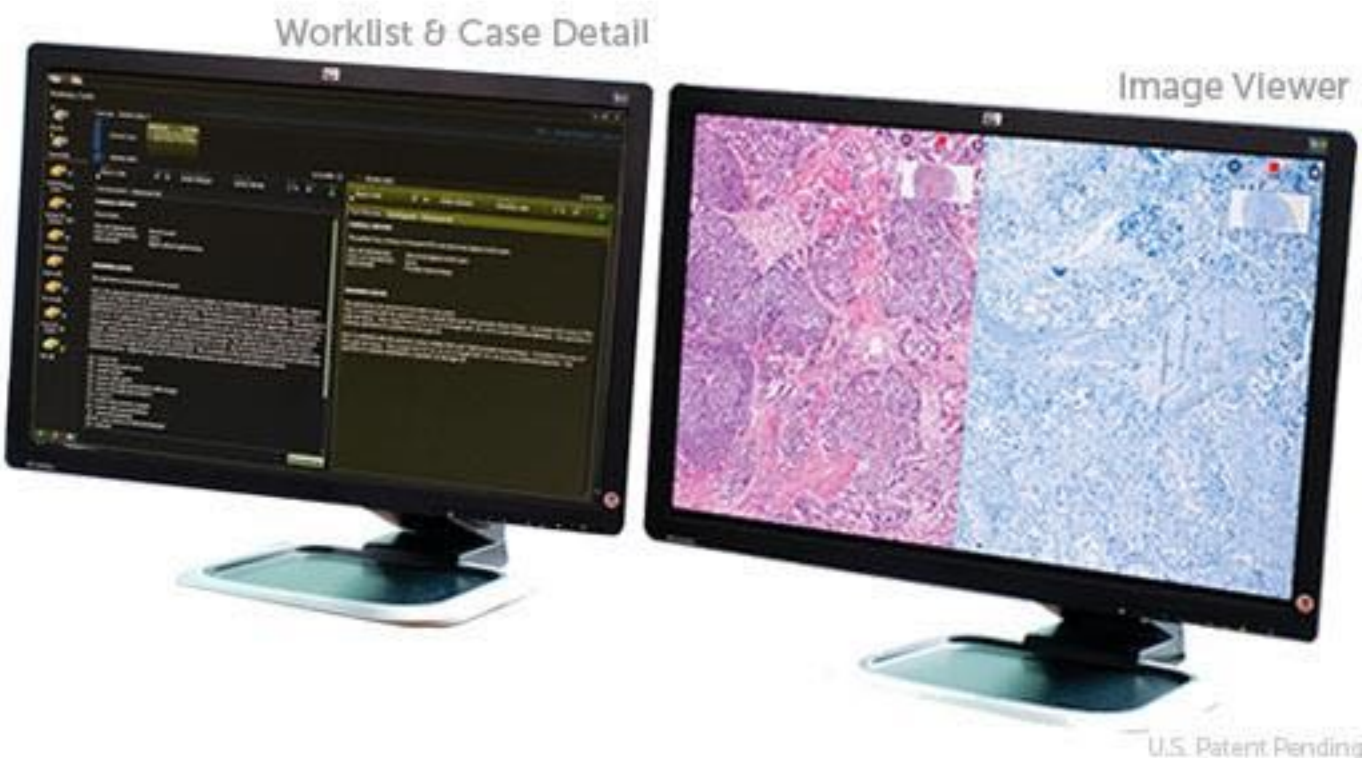
Digital pathology - Use in breast pathology reporting

Professor D Snead
UHCW NHS Trust Coventry
and
University of Warwick

Disclaimer

- Philips computational pathology board

Digital Pathology



UHCW Digital Pathology Validation Study

Did DP and LM give same diagnosis	Was DP and GS reported by same pathologist?		Total
	Yes	No	
Yes	981 (32.5%)	1964 (65%)	2945 (97.6%)
No			
No clinical difference	19 (0.6%) [11, 8]†	32 (1%) [14, 18]†	51 (1.7%) [25, 26]†
Clinical difference	9 (0.3%) [1, 8]†	12 (0.4%) [8, 4]†	21 (0.7%) [9, 12]†
Total	1009 (33.4%)	2008 (66.6%)	**3017**

† The numbers in [square] brackets correspond to the number of samples where the ground truth is provided by DP and GS respectively.

DP digital pathology, GS glass slides, LM light microscopy

Validation of digital pathology imaging for routine primary diagnosis

Snead, Rajpoot *et al.*, *Histopathology* (Jun 2016)

35,000 cases reported on digital pathology to date

Specialty	Cases
Breast	253
Dermatopathology	539
ENT	257
GIT	405
General pathology	487
Gynaecological	377
Lymphoreticular	166
Renal	94
Respiratory	197
Urology	242
Total	3017

Histopathology

Histopathology 2017, 70, 849. DOI: 10.1111/his.13210

Announcement

Roger Cotton *Histopathology* Prize 2016

DOI: 10.1111/his.13210

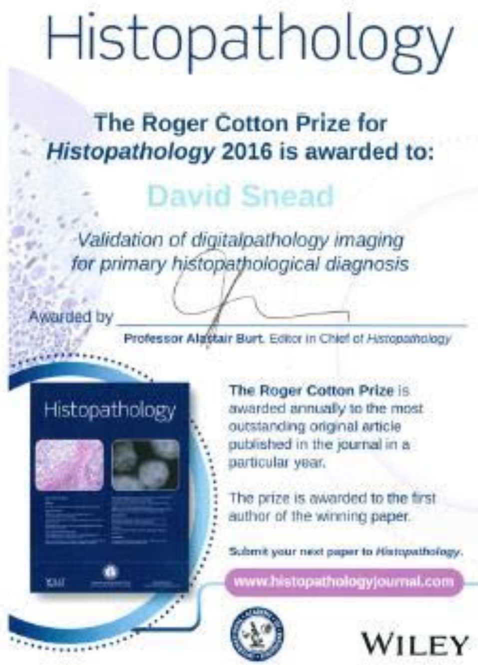
The journal continues its tradition of awarding the Roger Cotton prize for the most outstanding original article to be published in *Histopathology* in a particular year.

I am delighted to announce that the winner of the prize for 2016 is first author David Snead for the excellent paper "Validation of digital pathology imaging for primary histopathological diagnosis (*Histopathology* 2016; 68: 1063-1072)".

Congratulations to Dr Snead and his colleagues.

Alastair Burt
Editor

Main photo Left to right. K Gopalakrishnan, E Blessing, YW Tsang, B Sinha, DRJ Snead, S Read-Jones, P Matthews, S Sah. Insert bottom Left to right: P Kimani, Y Yeo, A Meskiri, IA Cree.



Memo from Public Health England
15 Sept 2016

Dear colleagues,

PHE is aware of rapid progress in clinical evaluation of digital pathology, and that several trusts are planning large scale implementation of this technology.

This is a very interesting development that may well offer future advantages for screening programme delivery. However, prior to implementation in a screening programme context, we need to be sure that it is at least equivalent to current methods. Therefore further evaluation, discussion and specification are required.

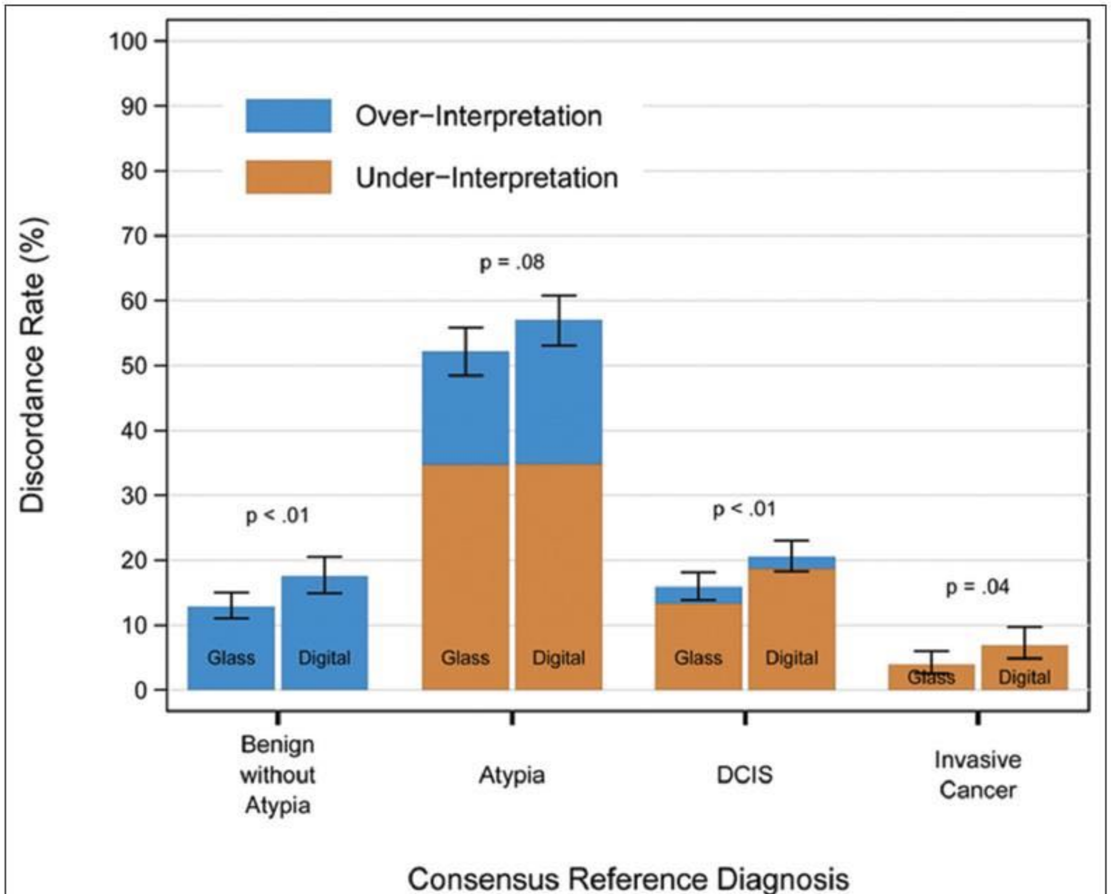
Please be aware that primary reporting of breast, bowel and cervical screening pathology specimens from a scanned slide should not currently be used.

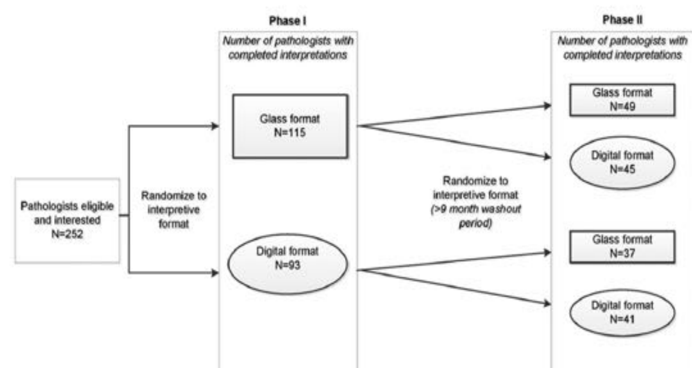
Further guidance on implementation will follow as soon as possible.

Research Article

A Randomized Study Comparing Digital Imaging to Traditional Glass Slide Microscopy for Breast Biopsy and Cancer Diagnosis

Joann G. Elmore[1], Gary M. Longton[2], Margaret S. Pepe[2,3], Patricia A. Carney[4], Heidi D. Nelson[5,6], Kimberly H. Allison[7], Berta M. Geller[8], Tracy Onega[9], Anna N. A. Tosteson[10], Ezgi Mercan[11], Linda G. Shapiro[11], Tad T. Brunyé[12], Thomas R. Morgan[1], Donald L. Weaver[13]





240 breast cases
4 sets of 60
1 slide per case

J Pathol Inform 2017;8:12.

Digital Pathology for the Primary Diagnosis of Breast Histopathological Specimens: An Innovative Validation and Concordance Study

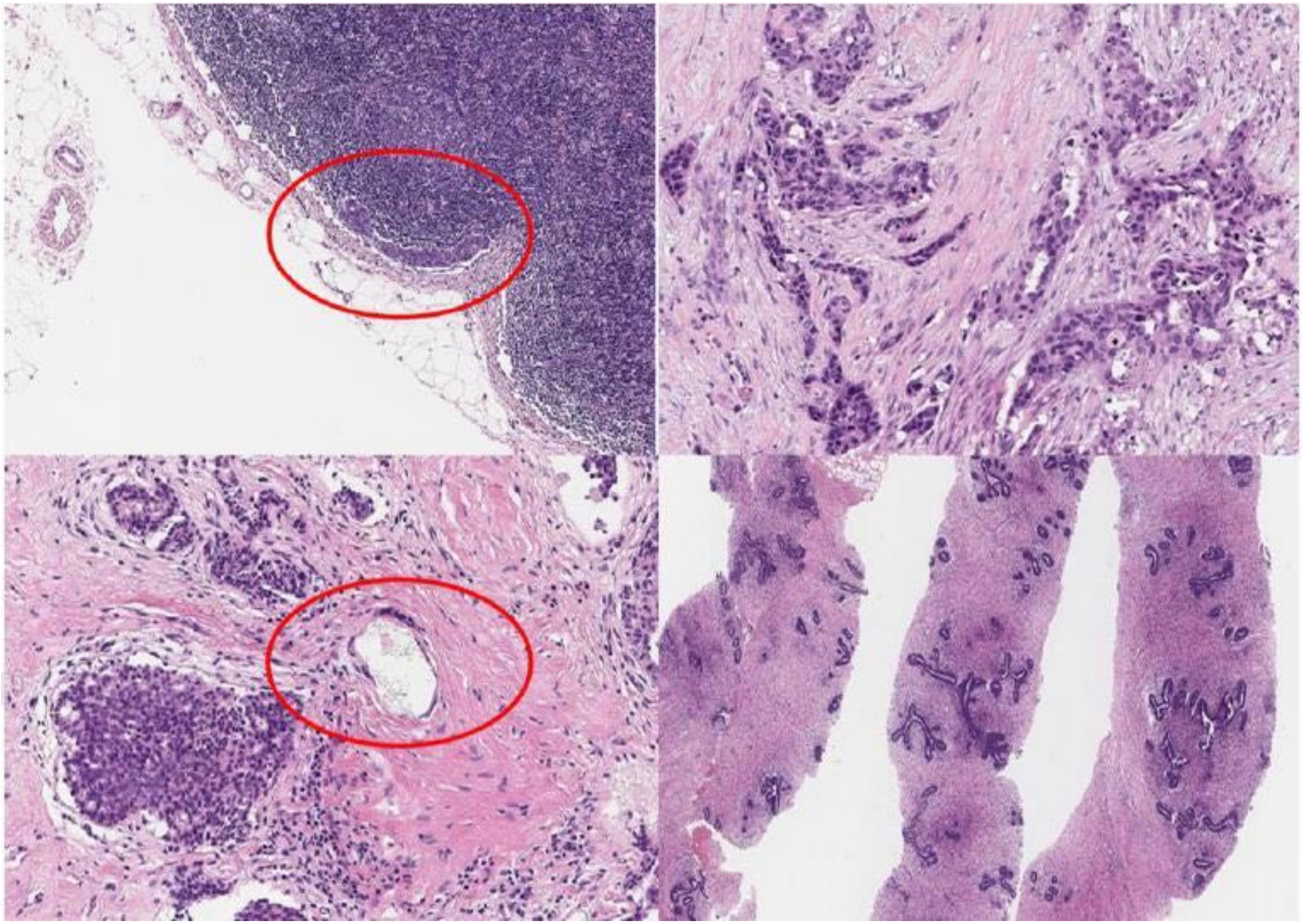
Digital Pathology Validation and Training

Dr Bethany Jill Williams[1], Prof. Andrew Hanby[1,2], Dr Rebecca Millican-Slater[1], Dr Anju Nijhawan[1], Dr Eldo Verghese[1,2], Dr Darren Treanor[1,2]

1. Department of Histopathology, Leeds Teaching Hospitals NHS Trust

2. University of Leeds

Diagnostic category	Number of cases
B1 (Normal tissue)	85
B2 (Benign lesion)	308
B3 (Lesion of uncertain malignant potential)	51
B4 (Suspicious)	5
B5a (Malignant – in situ)	43
B5b (Malignant- invasive)	145
LB1 (No lymphoid tissue)	1
LB2 (Benign lymphoid tissue)	22
LB5 (Malignant, metastatic carcinoma or other)	5
Other	29
Total	694



1.2% non concordance rate

Histopathology 2017

doi: 10.1111/his.13403

Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology

A Multicenter Blinded Randomized Noninferiority Study of 1992 Cases (Pivotal Study)

Benign/atypical core needle biopsy: 50
Benign/atypical lumpectomy: 50
In situ carcinoma core needle biopsy: 49
In situ carcinoma lumpectomy: 50
Invasive carcinoma core needle biopsy: 50
Invasive carcinoma lumpectomy: 50

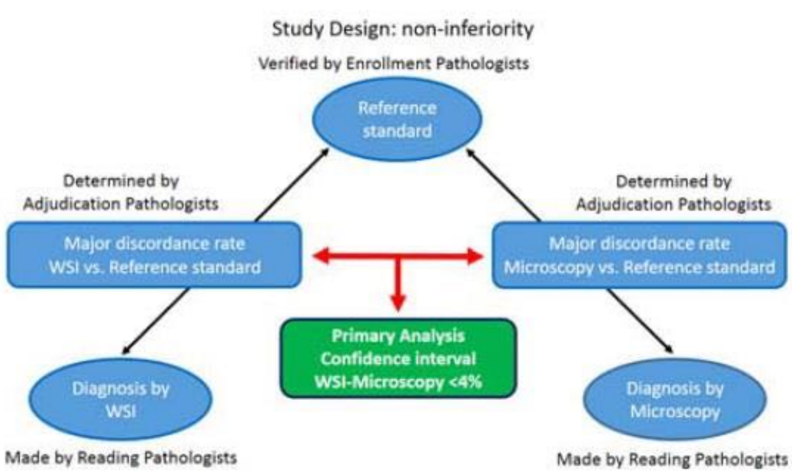
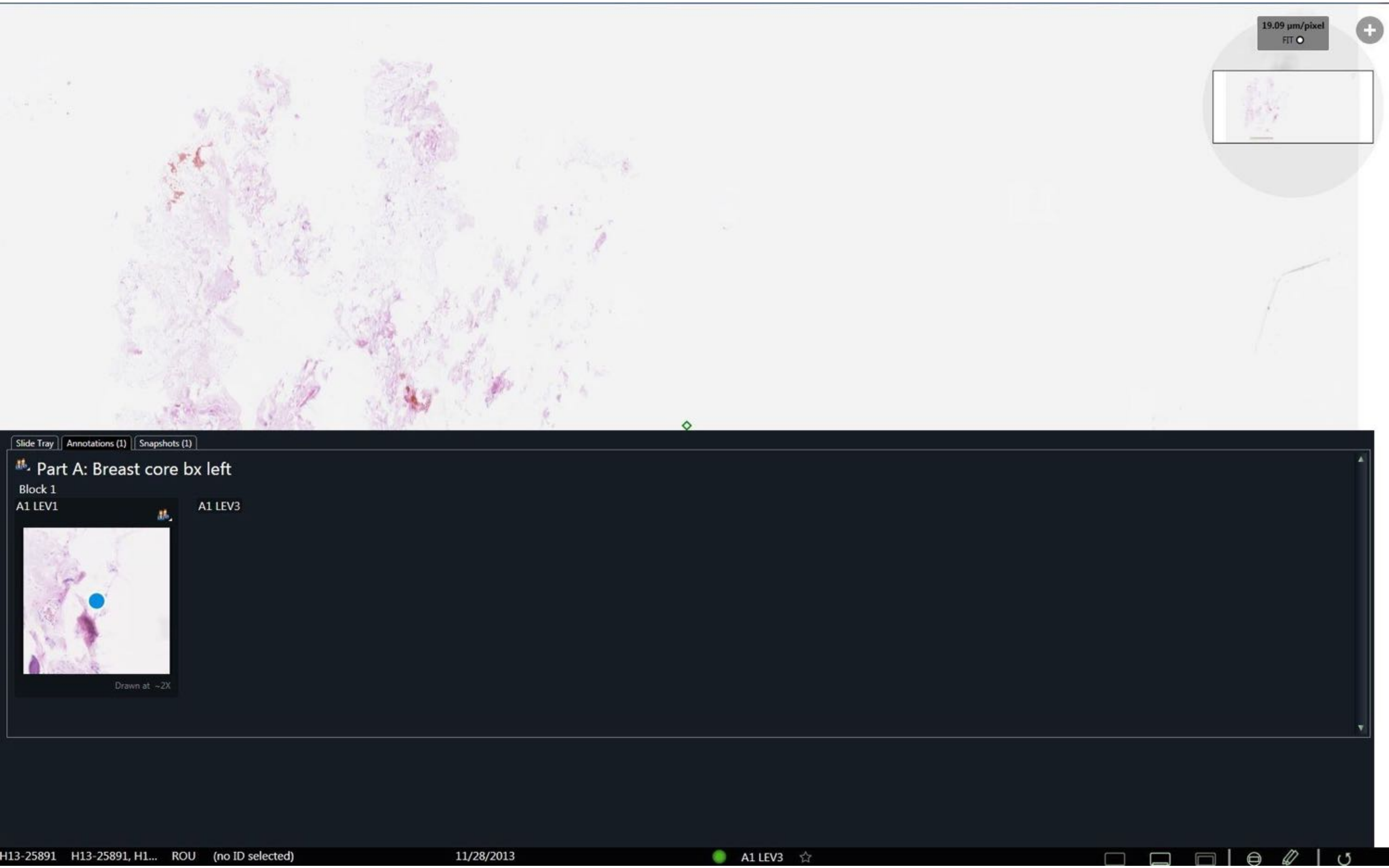
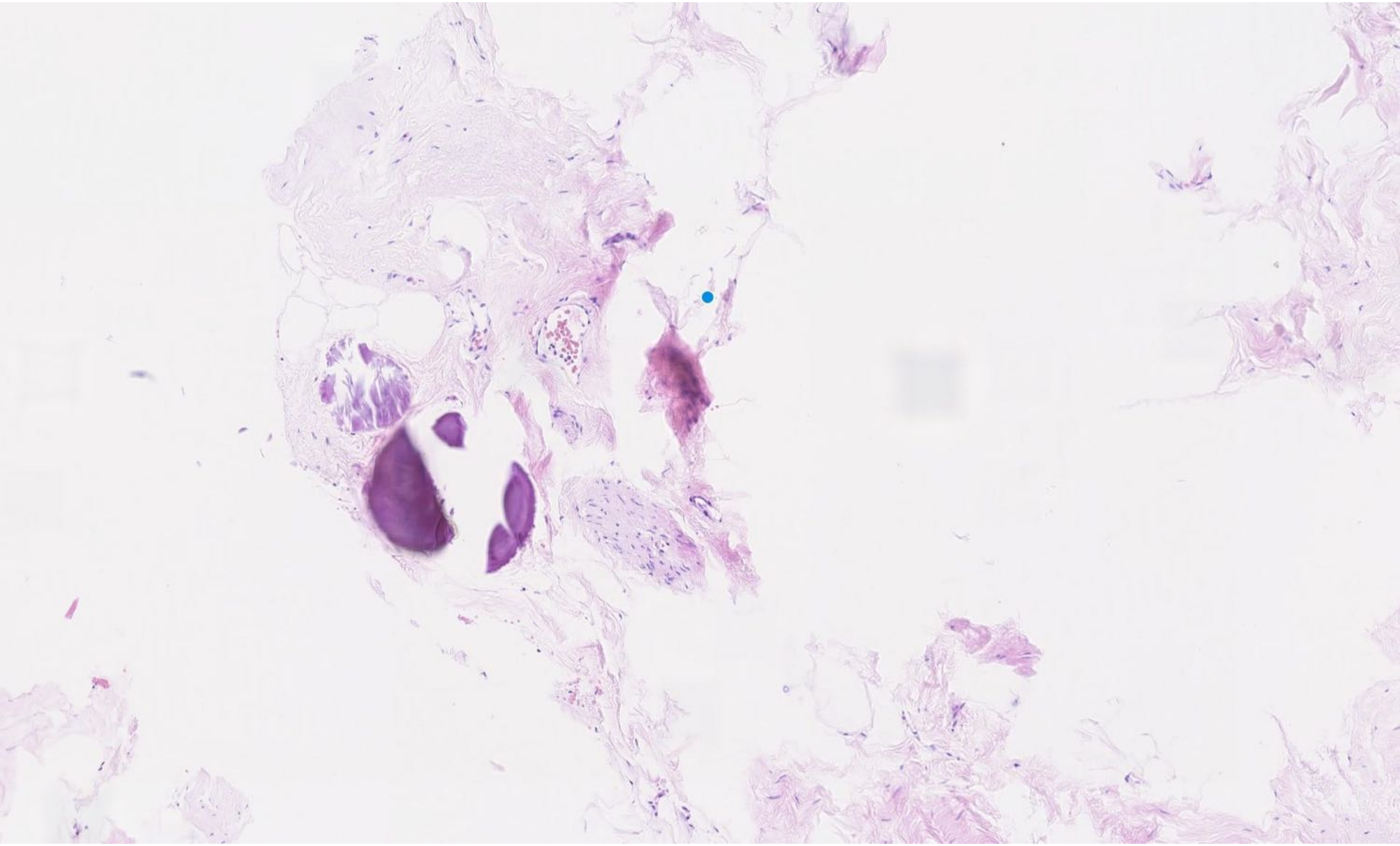


TABLE 3. Major Discordance Rates by Organ System: Microscopy Versus Reference Standard and WSI Versus Reference Standard

Major Discordance Rate	Between Microscopy and Reference Standard (%)	Between WSI and Reference Standard (%)
$<1\%$	Peritoneal (0)	Peritoneal (0)
	Gallbladder (0)	Gallbladder (0)
	Appendix (0)	Appendix (0)
	Soft tissue (0)	Soft tissue (0)
	Stomach (0.5)	Lymph node (0.3)
	Lymph node (0.8)	Stomach (0.8)
1%-4.9%	Colorectal (1)	Peri(anal) (1)
	Kidney neoplastic (1)	Colorectal (1.7)
	Gastroesophageal junction (1.3)	Salivary gland (2)
	Peri(anal) (2)	Gastroesophageal junction (2)
	Salivary gland (3)	Kidney neoplastic (2.5)
	Respiratory (4.2)	Respiratory (3.5)
	Breast (4.3)	Breast (4.2)
	Skin (4.7)	Liver/bile duct (4.6)
	Endocrine (4.7)	Skin (4.9)
$\geq 5\%$	Gynecologic (5.2)	Brain (6.2)
	Liver/bile duct (5.6)	Gynecologic (6.3)
	Brain (5.8)	Endocrine (6.5)
	Bladder (6.1)	Bladder (7.3)
	Prostate (11.3)	Prostate (12)


19.09 µm/pixel
FIT
Slide Tray
Annotations (1)
Snapshots (1)
Part A: Breast core bx left
Block 1
A1 LEV1
A1 LEV3
Drawn at ~2X
H13-25891
H13-25891, H1...
ROU
(no ID selected)
11/28/2013
A1 LEV3



Challenges for routine practice

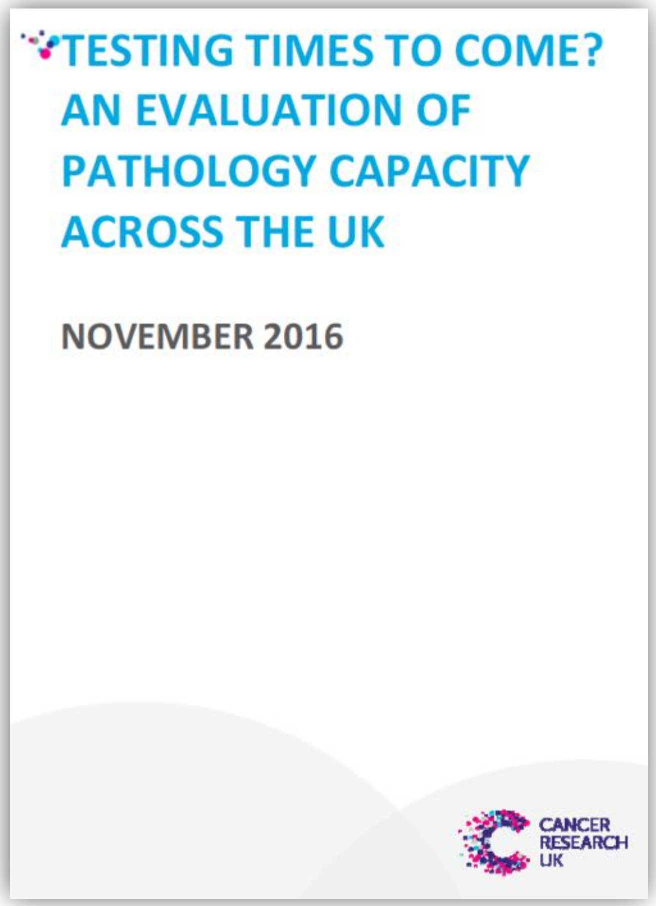
- Front and back end interface with LIMS needed
- Develop scanning rules
- Re-work laboratory protocols
- Improve section quality and tissue mounting
- Maintain streaming speed within the departmental security protocol
- Some things will still need glass
  - Polarisation
  - Cytology
  - Over sized blocks
  - Low grade dysplasia
  - X100 oil (scanty organisms)

H17 49105
D
H17 49105
E
H17 49105
F
H17 49159
H17 49176
G17 44348


UHCW Pressure Ulcer Prevention Week
The Tissue Viability Team is calling for all clinical staff to pledge to...
KEEP ON ASKIN
Assess
Surface
Keep moving
Incontinence
Nutrition
What can YOU do to PREVENT PRESSURE ULCERS?
Visit the home page on TrustNav to find out about pressure ulcer prevention's Six Moments
TOM-11
DO NOT OPERATE OR PAT TEST WITHOUT WATER

Crisis in pathology staffing

- 26% consultant posts vacant at the moment
- 32% of consultants over 55 (615 due to retire in next 5 years)
- Many departments already send away cases
- Complexity of early cancer detection
- Escalation of molecular testing and companion diagnostics
- Number of octogenarians is set to double in next 10 years


TESTING TIMES TO COME? AN EVALUATION OF PATHOLOGY CAPACITY ACROSS THE UK

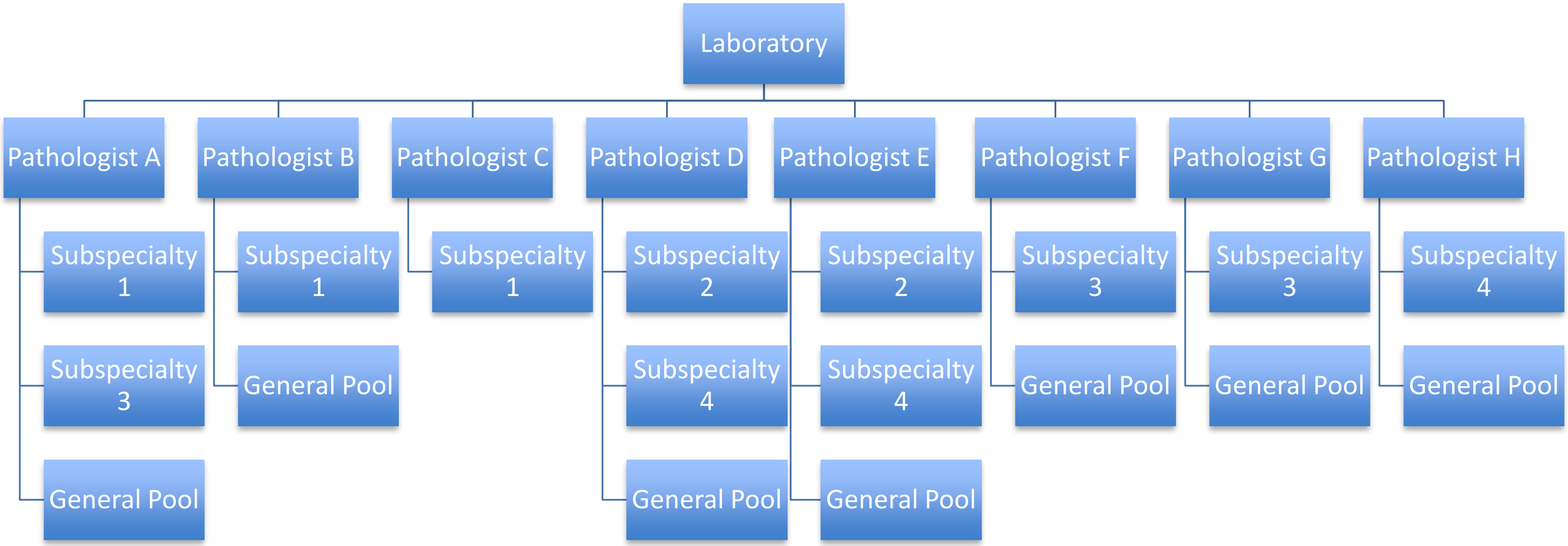
NOVEMBER 2016

CANCER RESEARCH UK

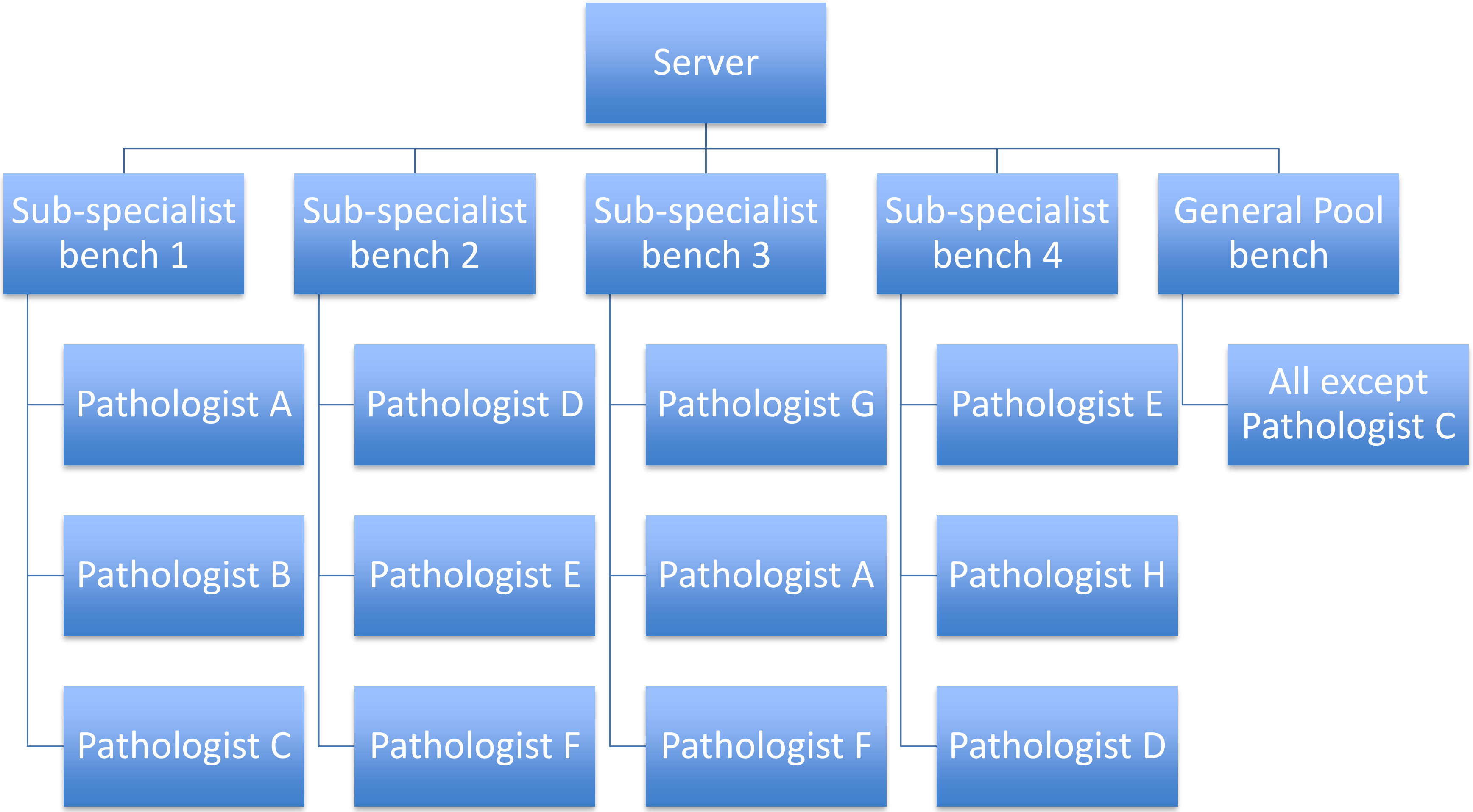
What does digital pathology offer?

- Economic advantages
  - Increase efficiency of pathologists
  - Reduce turn around time to report cases
  - Improved review of cases including MDT/Tumour board review
- Quality advantages
  - Reduced error rate
  - Increased subspecialisation
  - IHC scoring and indexing
  - Tumour grading / dysplasia grading
  - Cancer finder

Pre-allocation of specimens
Push system



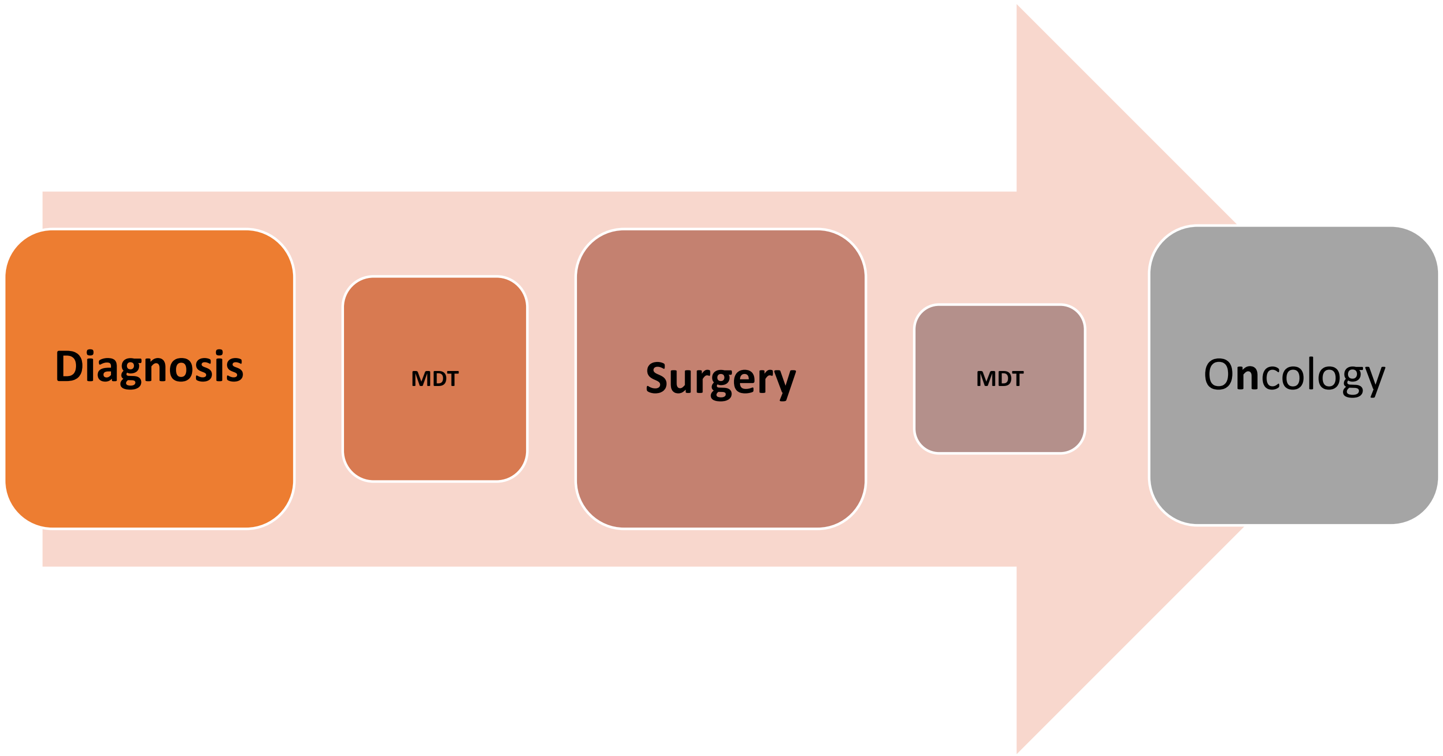
Improved workflow efficiency
Pull system

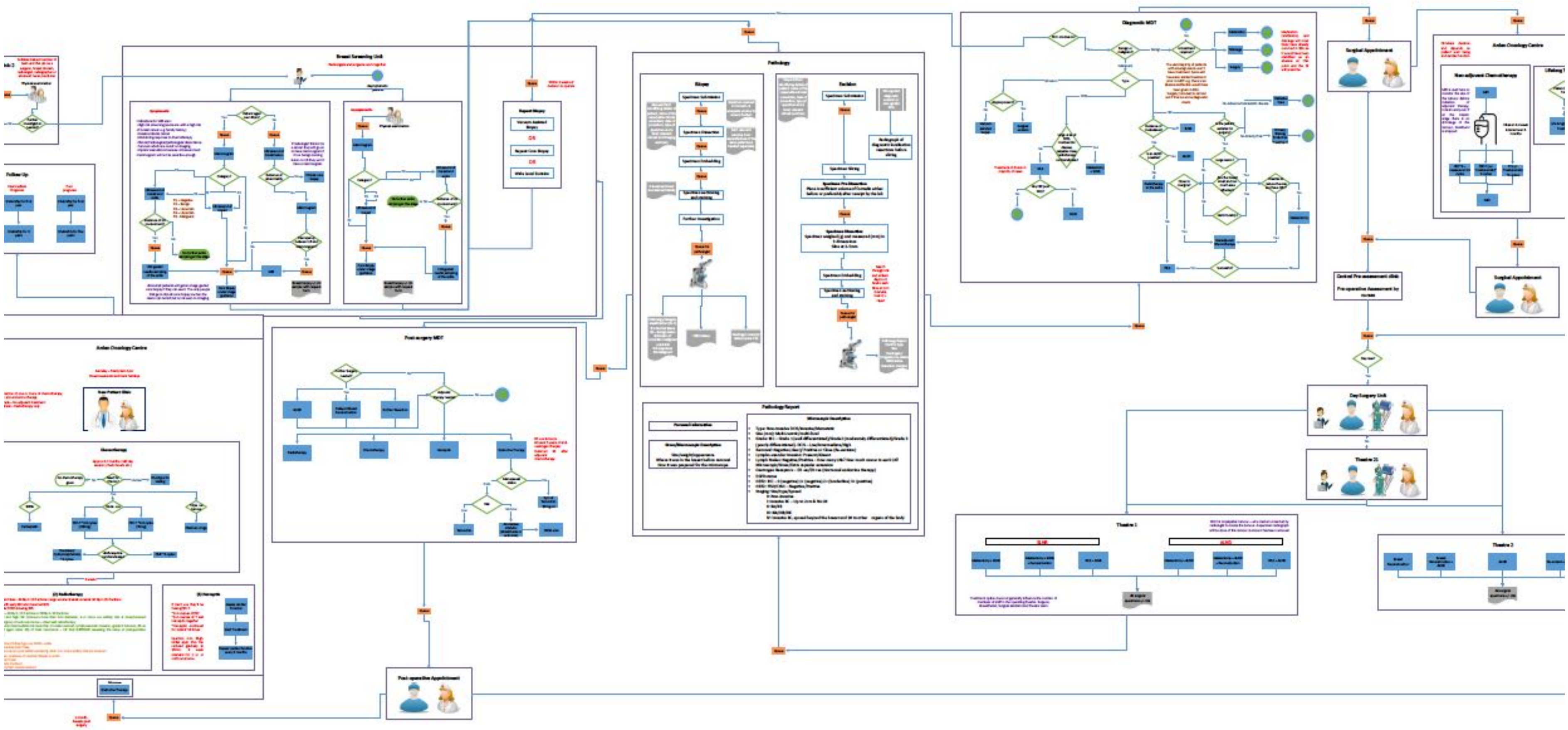


Remote reporting

- Workstations fitted with remote access to VPN
- RSA token remote login
- Ultra and Omnyx accessed through VPN
- Dragon voice recognition installed on workstation
- Backlogged cases available to report
- Report entered in and authorised
- Additional requests made via LIS

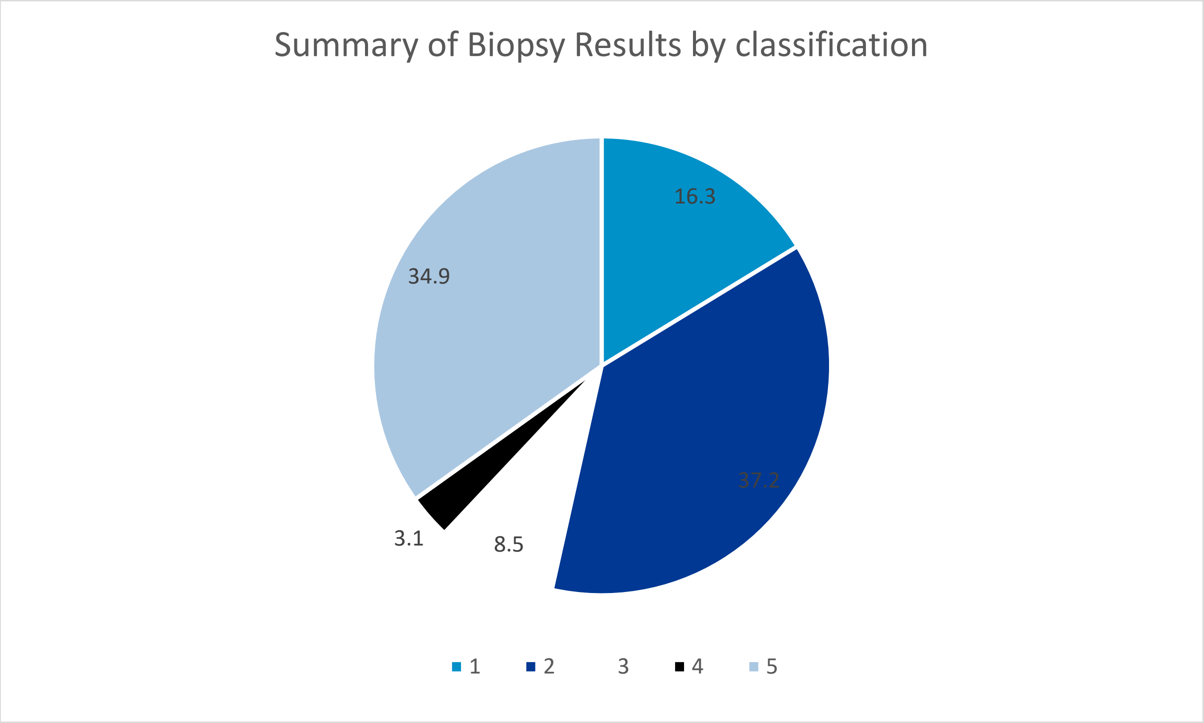
Breast cancer pathway outline





Breast Screening Unit
Pathology
Biopsy
Excision
Pathology Report
Diagnostic MDT
Surgical Appointment
Post-surgery MDT
Post-operative Appointment
Day Surgery Unit
Theatre 1
Theatre 2
Follow Up

Breast core biopsies by result category

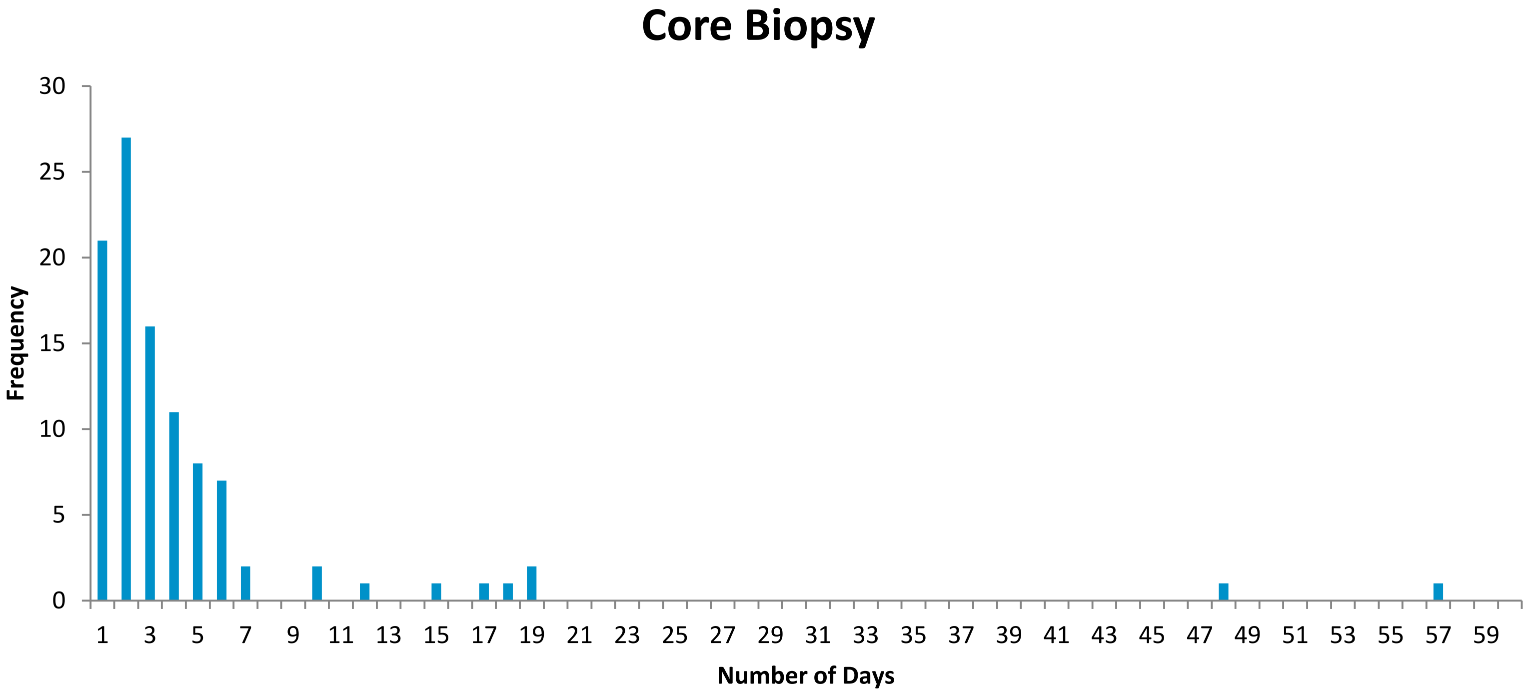


N=233

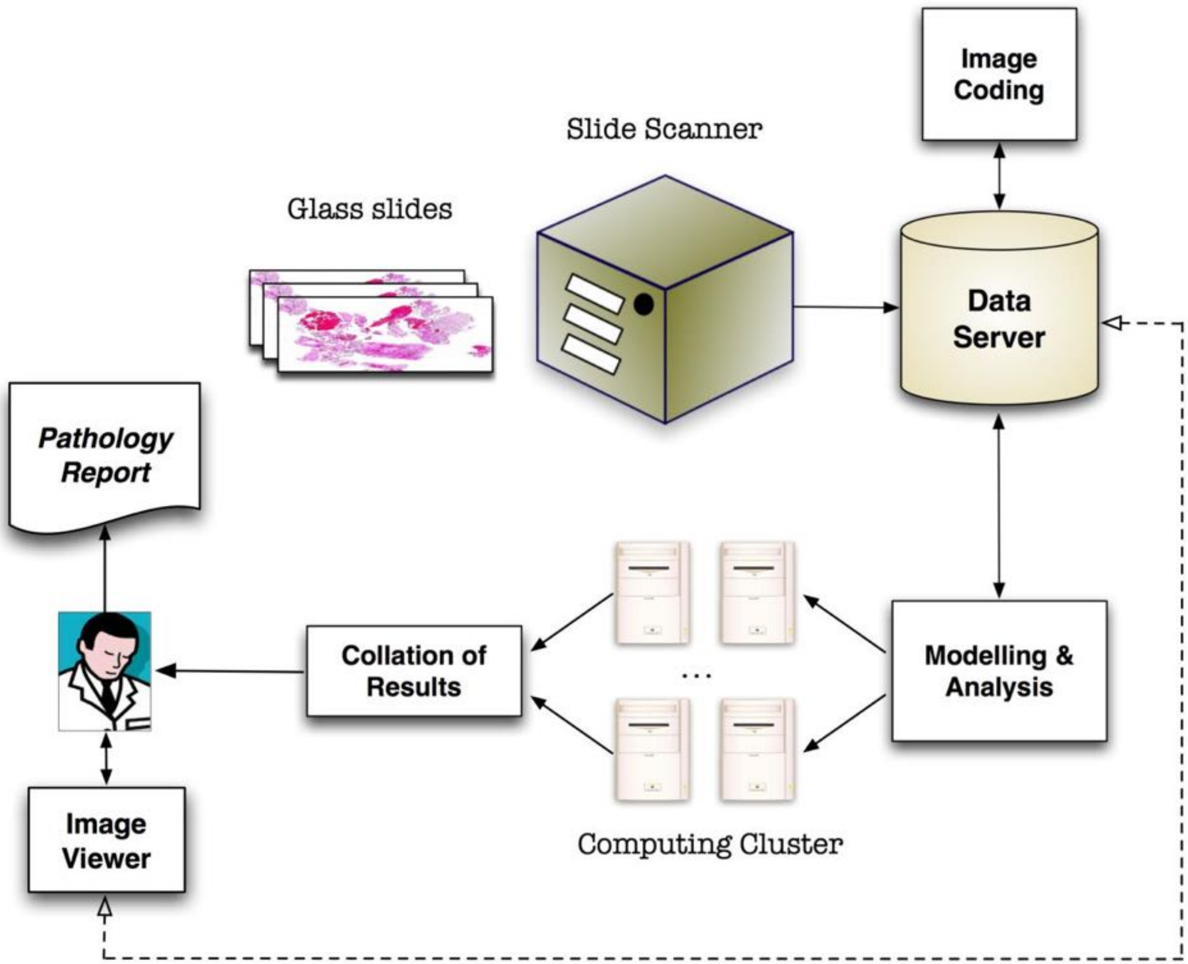
Indeterminate core biopsies

Patient	Core biopsy	Vacora Biopsy	Surgical biopsy	WLE
1	B3		B3	
2	B3	B1/B2		
3	B3		DCIS	
4	B3	B3		B2
5	B3		B2	
6	B4	B5a		High grade DCIS
7	B3	B2		
8	B3		B1	
9	B3/4	B3		
10	B3		B1	
11	B3		B2	
12	B4	B5b		Grade 2 Ductal
13	B4			

Breast core biopsy time to final report



PathCAD Systems



Digital pathology algorithms – main applications

- IHC Biomarker assessment
  - ER, PR, HER2 & Ki67
- Disease quantification and grading tools
  - Cancer grading tools bladder, breast and prostate cancer
  - Dysplasia grading tools cervix, head and neck
- Rare event detection tools
  - Prostate template biopsies
  - Sentinel lymph node biopsies
- Automation
  - IHC Biomarker assessment
  - Endoscopic biopsies

The Digital Pathology Market

2012 → $2.1 bn, 2013 → $2.2 bn, … **2018 → $4.5 bn**

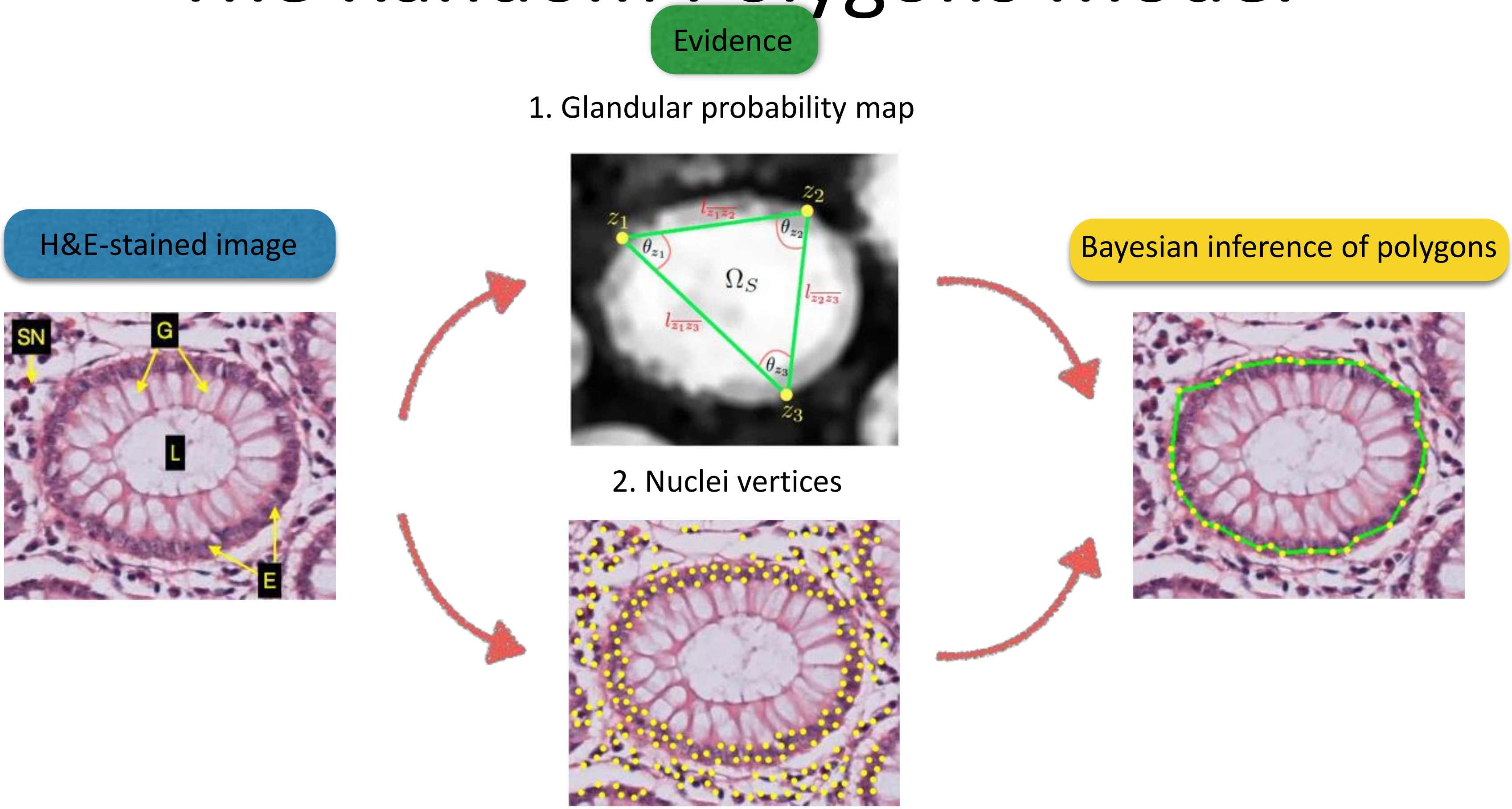
(14.7% compound annual growth)

Report Overview

Digital Pathology: Technologies and Global Markets

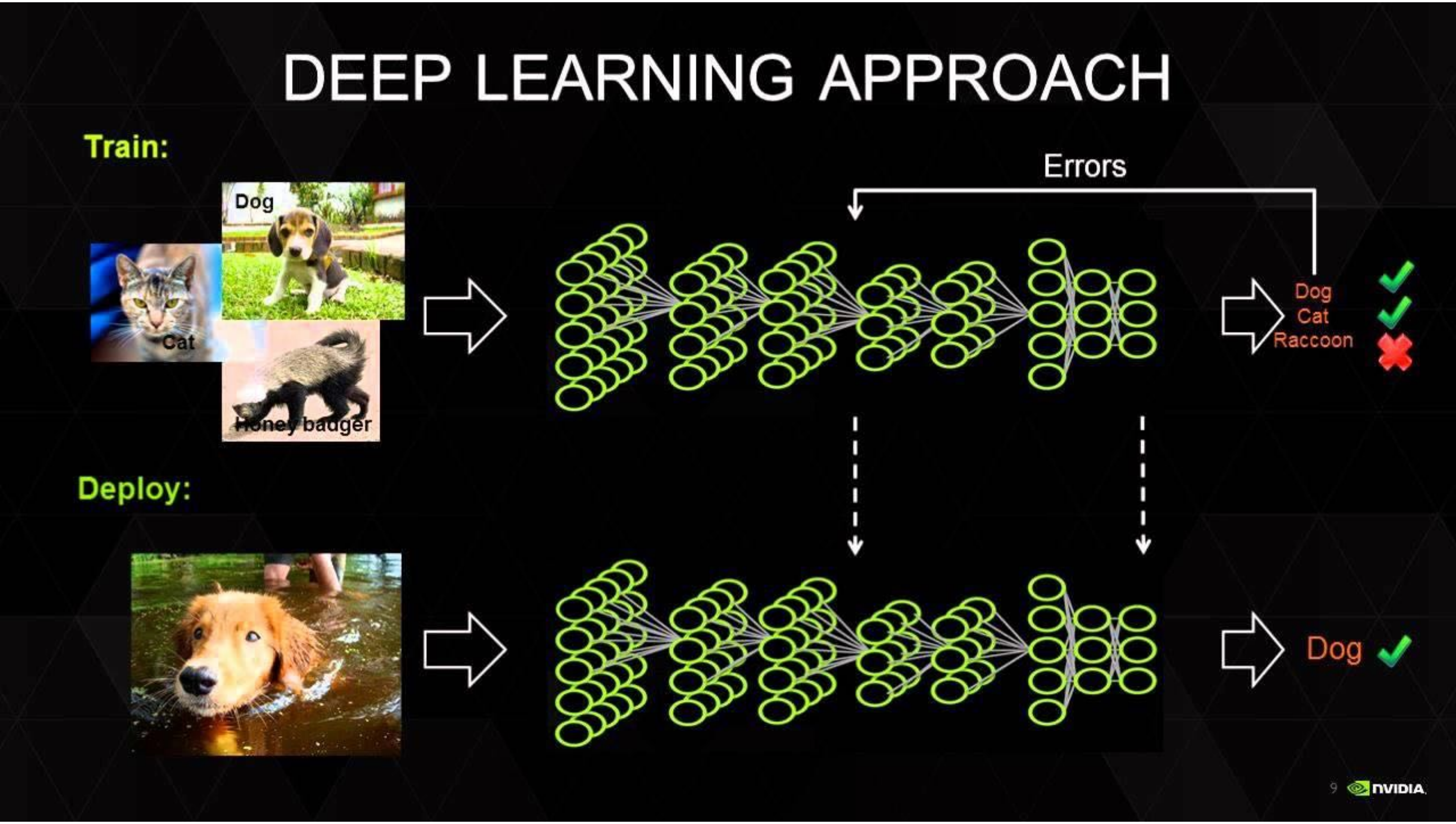
Feb 2014 • HLC161A

Tubule formation
The Random Polygons Model



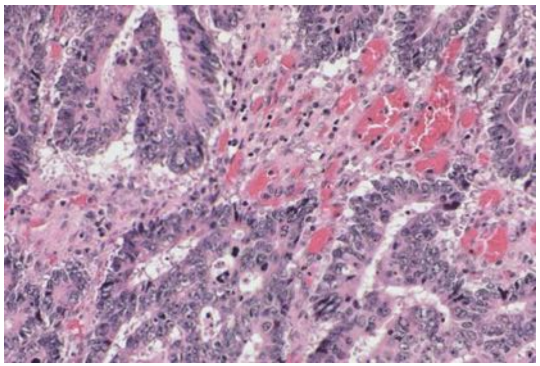
Sirinukunwattana *et al.*, IEEE *Trans Med Imaging* (Nov 2015)

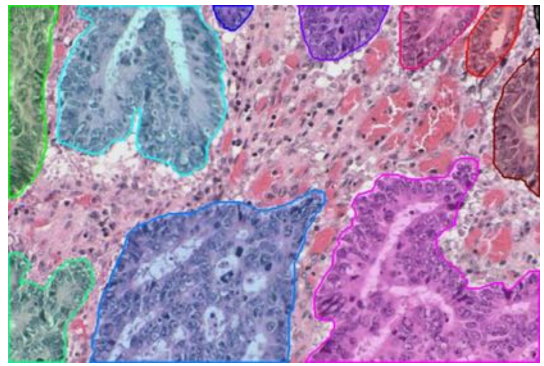
US patent application number 61452293

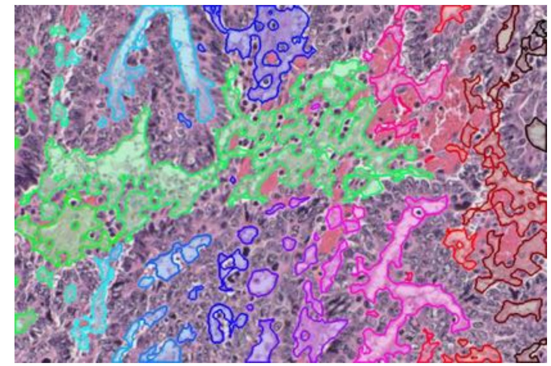

DEEP LEARNING APPROACH
Train:
Dog
Cat
Honey badger
Errors
Dog
Cat
Raccoon
Deploy:
Dog
9
NVIDIA

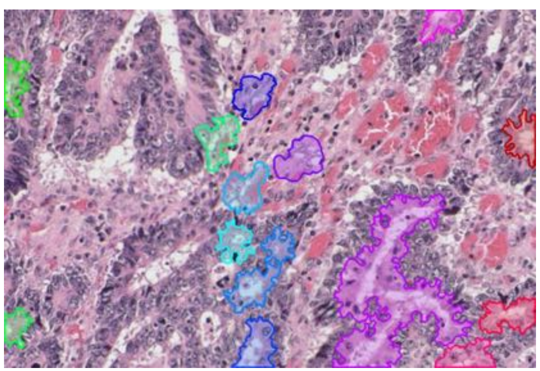
Experimental Results

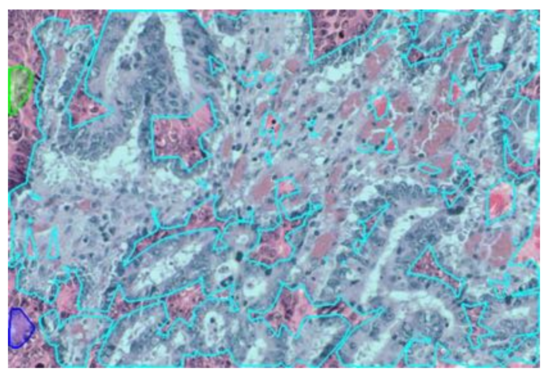
Experiment: Warwick-QU Dataset (moderately & poorly differentiated tumor samples)

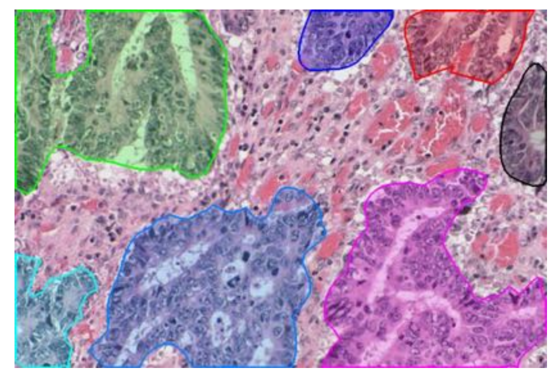

H&E-stained image


ground truth


Farjam et al.

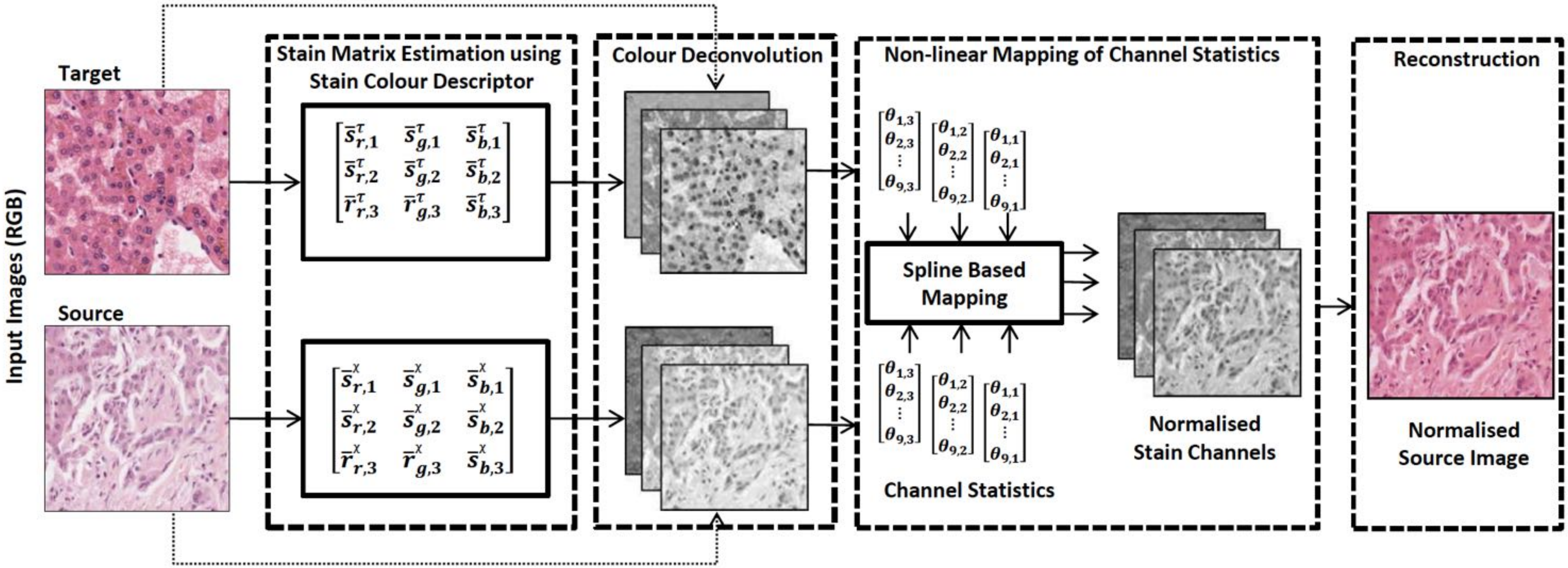

Naik et al.


Nguyen et al.


RPM

Sirinukunwattana *et al.*, IEEE *Trans Med Imaging* (Nov 2015)

Stain Normalization



A non-linear mapping approach to stain normalisation

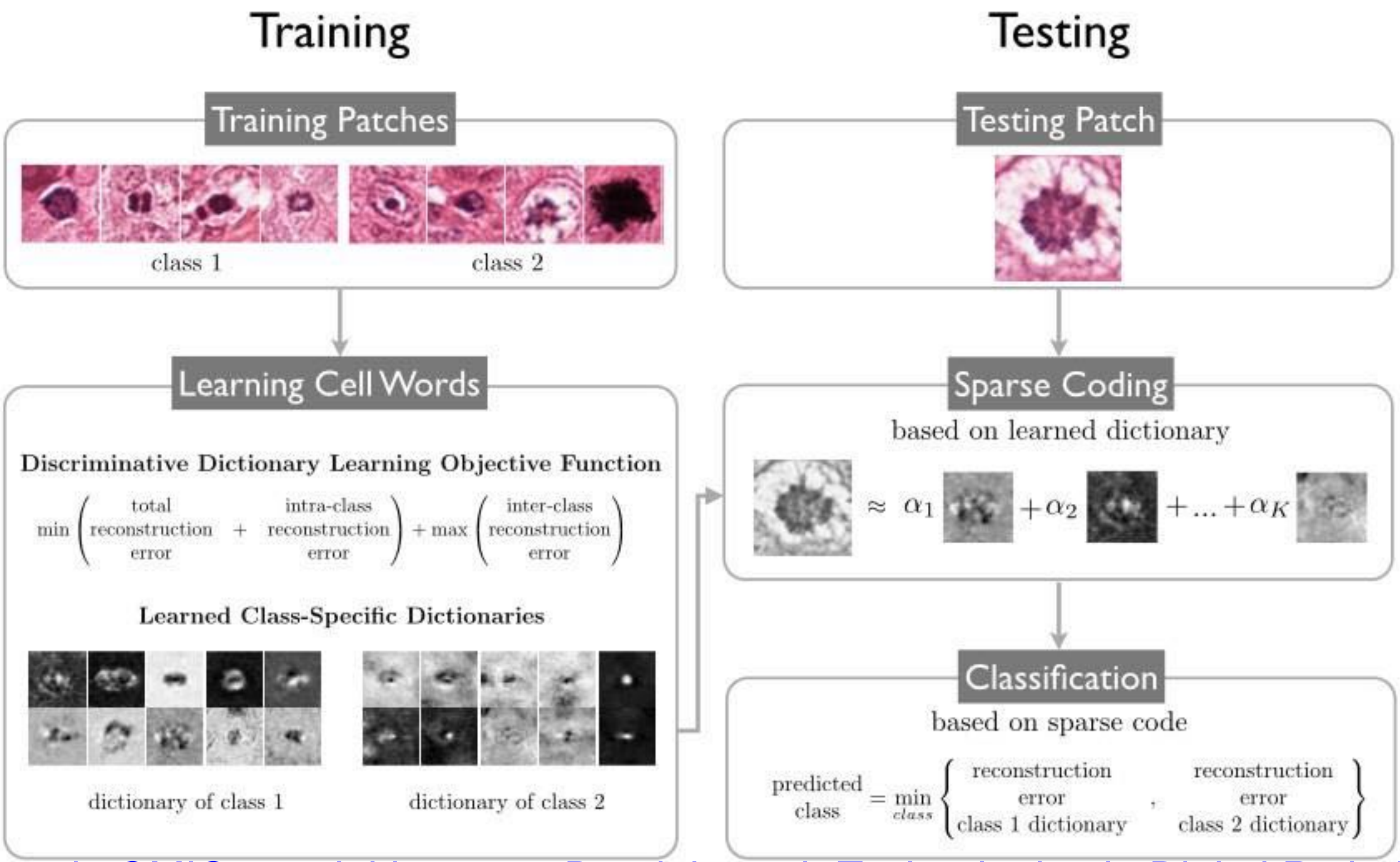
Khan *et al.*, *IEEE Transactions on Biomedical Engineering* (2014)

Stain Normalization Toolbox

Publicly available toolbox consisting of some of the leading algorithms (including our own) for normalization of stain colors in histology images

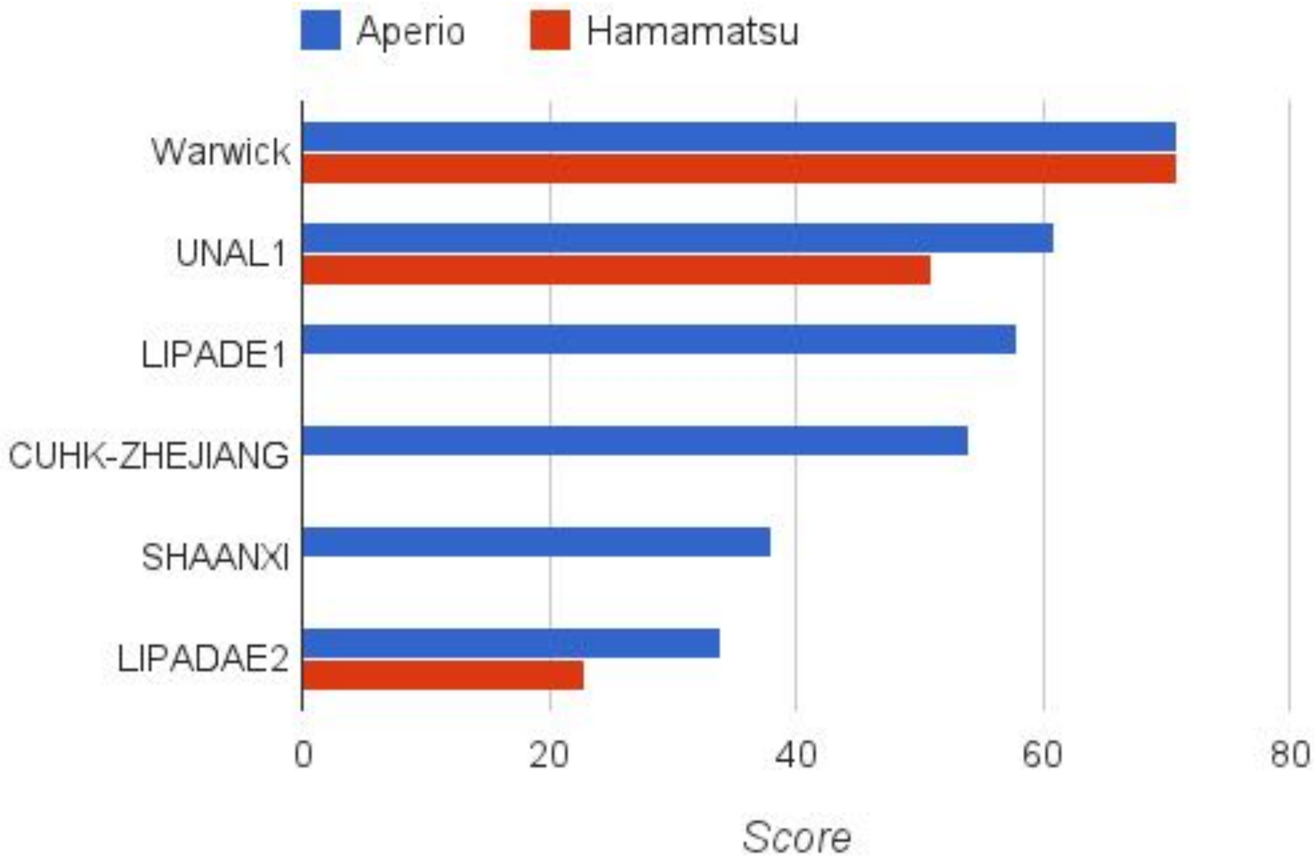
http://www.warwick.ac.uk/bialab/software/sntoolbox

Mitosis algorithm



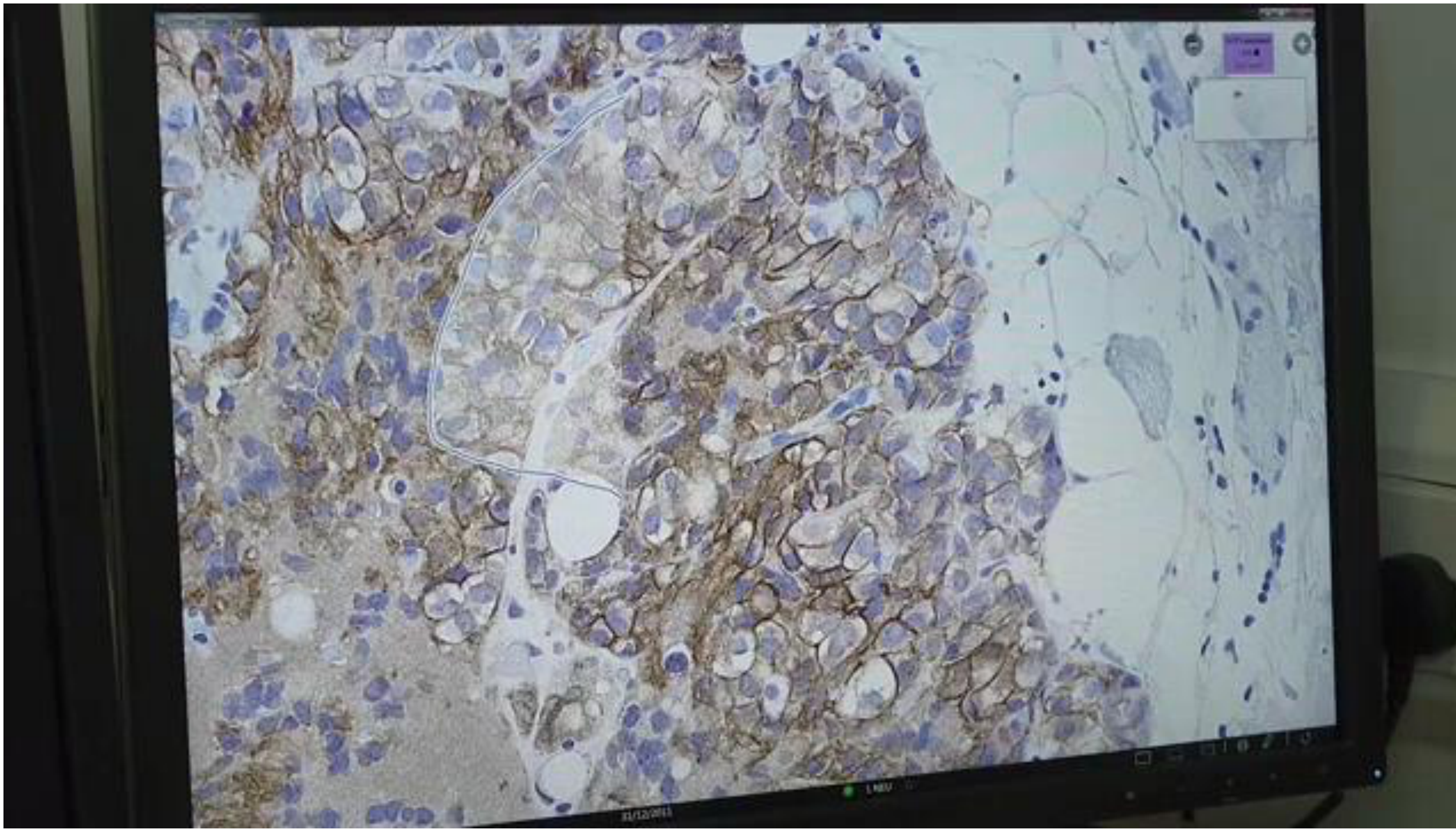
Khan *et al., CMIG special issue on Breakthrough Technologies in Digital Pathology* (2015)

MITOS-ATYPIA Challenge Contest



Winner of the MITOS-ATYPIA Grand Challenge Contest at ICPR'2014

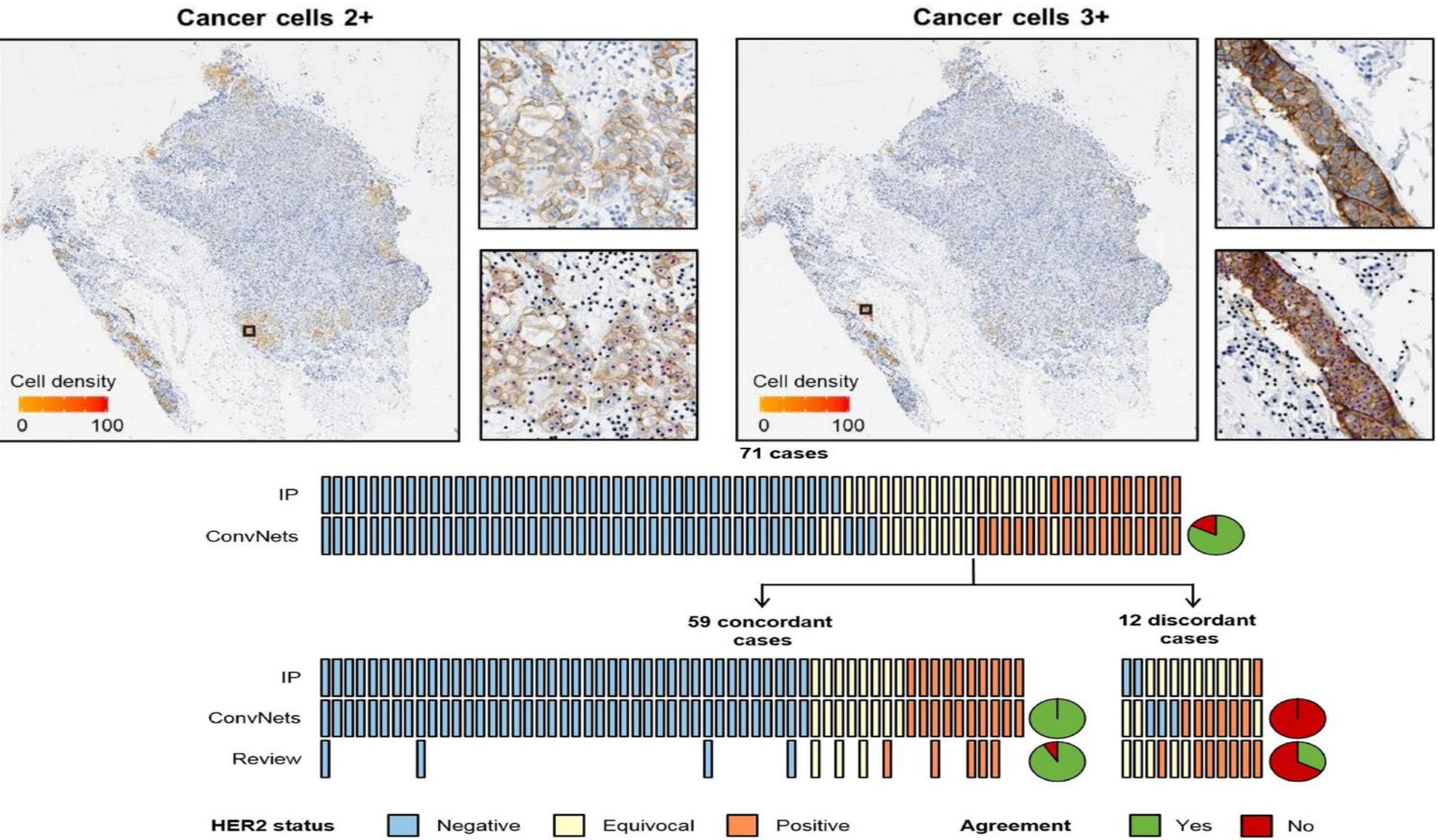
http://mitos-atypia-14.grand-challenge.org/results2/



Relevance of deep learning to facilitate the diagnosis of HER2 status in breast cancer

SCIENTIFIC REPORTS | 7:45938 | DOI: 10.1038/srep45938

Michel E. Vandenberghe[1], Marietta L. J. Scott[1], Paul W. Scorer[1], Magnus Söderberg[2], Denis Balcerzak[1] & Craig Barker[1]



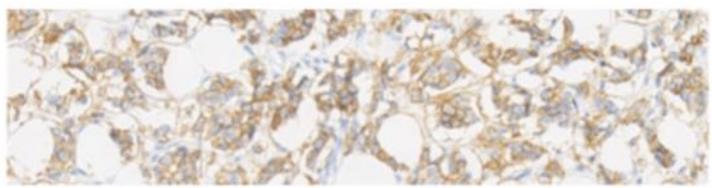
Automated Her2 Scoring

Pathological Society
Understanding Disease

Her2 Scoring Contest

Home | Background | Contest Registration | Contest Rules| Contact

HER2 Contest



Welcome to the contest page of **HER2 scoring in histology images.** This challenge will be held in conjunction with Nottingham Pathology 2016 (The Pathological Society of Great Britain & Ireland).

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

UCLM
UNIVERSIDAD DE CASTILLA-LA MANCHA

University Hospitals Coventry and Warwickshire NHS Trust

AIDPATH
http://aidpath.eu

http://www.warwick.ac.uk/TIAlab/Her2Contest

Qaiser et al., Histopathology (in press)

Her2 Scoring – Man *vs* Machine

Rank	Team Name	Score	Bonus	Score+Bonus
1	**Team Indus**	**220**	**12.5**	**232.5**
2	**Pathologist 2**	**210**	**20.5**	**230.5**
3	Visilab	212.5	15	227.5
4	MUCS (Ireland)	205	20.5	225.5
5	Pathologist 1	185	10	195
6	Pathologist 3	180	13	193

http://www.warwick.ac.uk/TIAlab/Her2contest/

Qaiser et al., Histopathology (in press)

CAMELYON16

ISBI Challenge on cancer metastases detection in lymph node

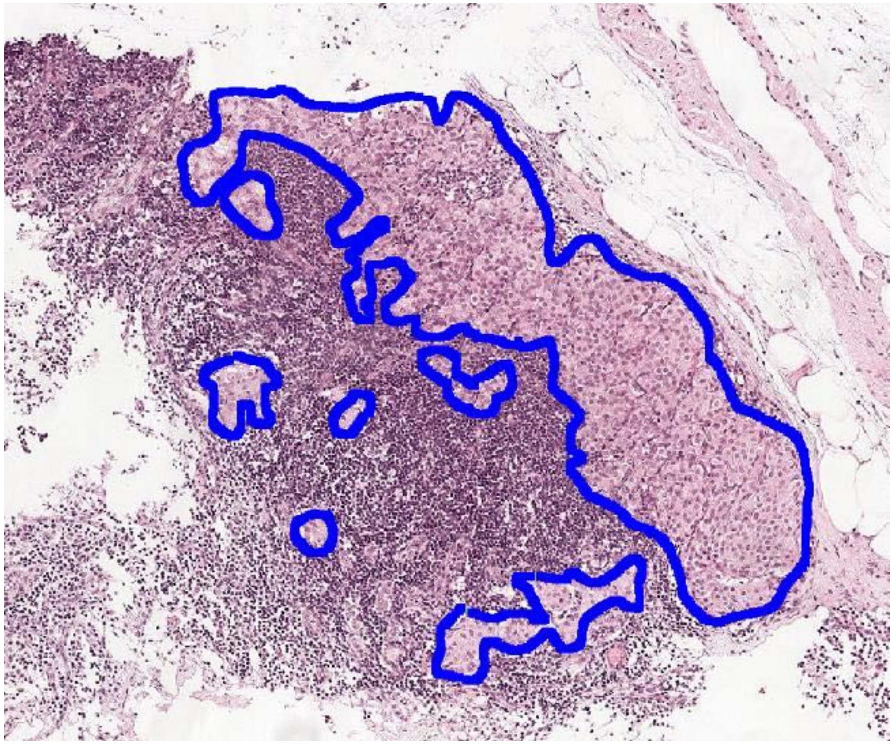
Babak Ehteshami Bejnordi

Prague
IEEE
IEEE Signal Processing Society

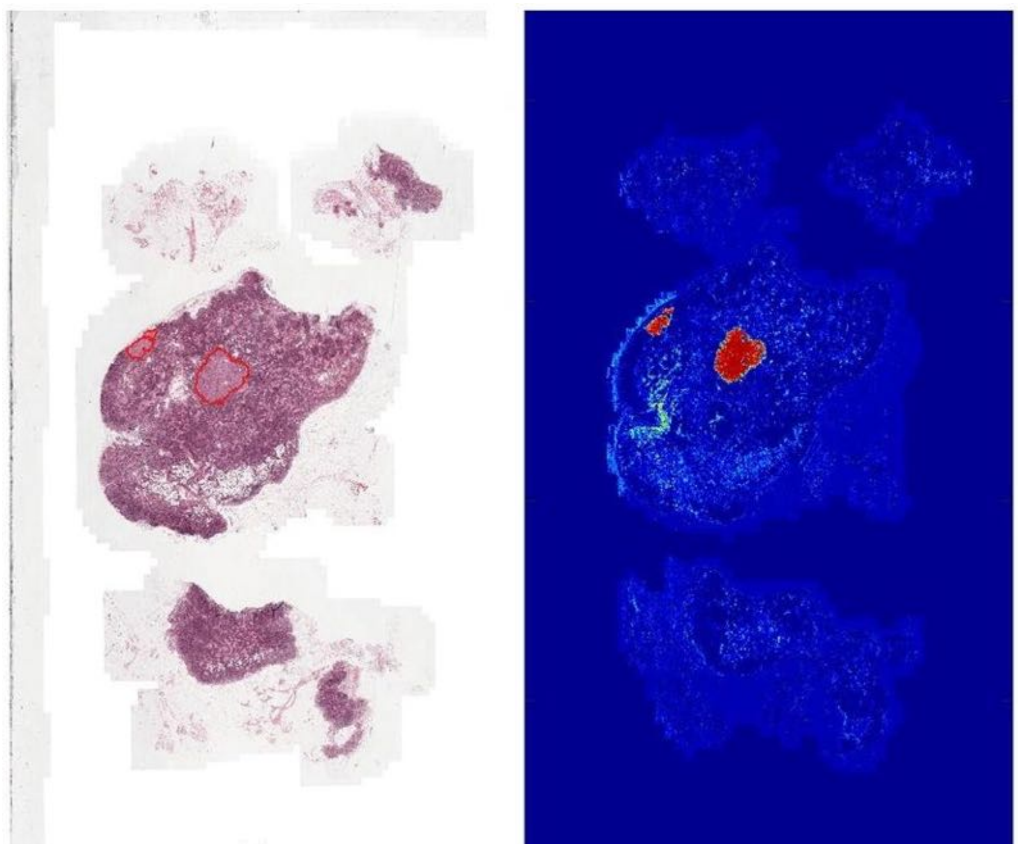
Radboudumc university medical center
UMC Utrecht
TU/e Technische Universiteit Eindhoven University of Technology
Where innovation starts
PHILIPS innovation + you
trait a ctmm project
ST IT PRO stichting IT projecten

Camelyon16 dataset

- Most of the tumor slides were exhaustively annotated
- The average time for annotating each slide was 1 hour



Locating Metastasis in Breast LNBs



(a) (b)

Qaiser, Rajpoot et al., *submitted*

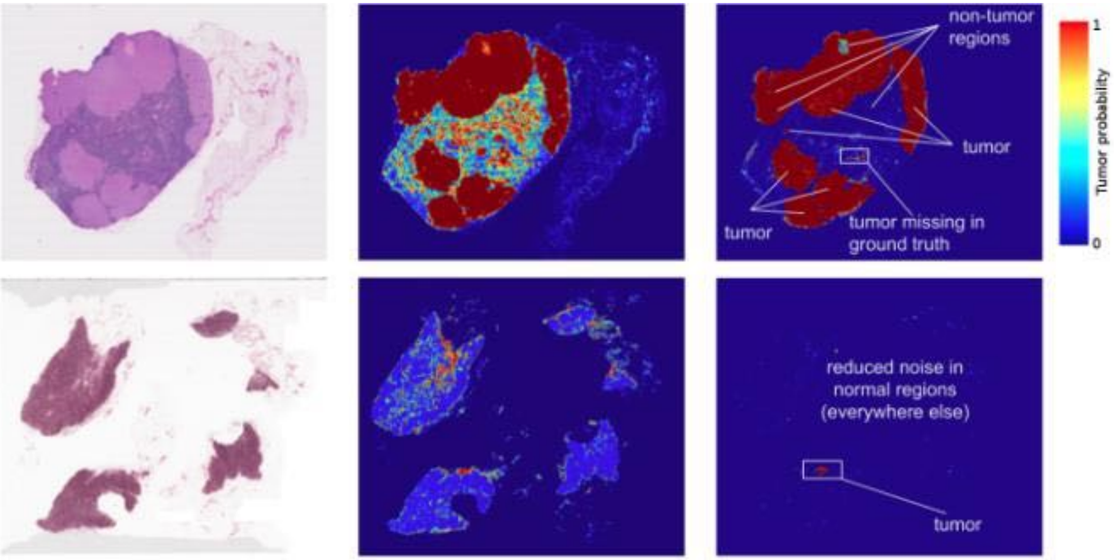
Google Research Blog

The latest news from Research at Google

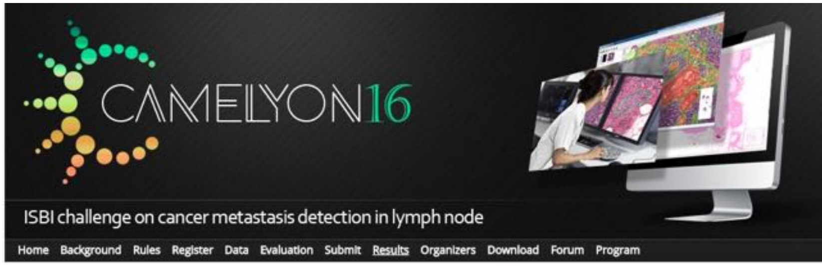
Assisting Pathologists in Detecting Cancer with Deep Learning

Friday, March 03, 2017

Posted by Martin Stumpe, Technical Lead, and Lily Peng, Product Manager



Left: Images from two lymph node biopsies. **Middle**: earlier results of our deep learning tumor detection. **Right**: our current results. Notice the visibly reduced noise (potential false positives) between the two versions.



Radboudumc | UMC Utrecht | PHILIPS innovation + you | trait a ctmm project | ST (T) PRO

MailOnline

Could computers diagnose cancer? Artificial intelligence shown to spot early signs of a tumour with 92 per cent accuracy

- Machine can sift millions of cells to spot just a handful of malignant ones
- AI algorithm was trained using slides of samples of patients lymph nodes
- Human pathologists can diagnose breast cancer with 96 per cent accuracy
- When the machine and human combined, accuracy went to 99.5 per cent

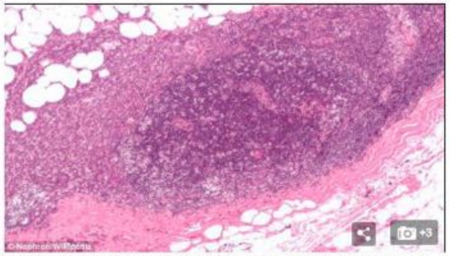
By RICHARD GRAY FOR MAILONLINE
PUBLISHED: 13:05, 20 June 2016 | UPDATED: 13:11, 20 June 2016

Share 60 shares 5 View comments

Computers could soon be helping to diagnose cancer in patients with the help of artificial intelligence that has been trained to spots the early signs of the disease.

An AI machine capable of accurately diagnosing breast cancer 92 per cent of the time has been developed by researchers.

While it is still not quite as good as human specialists – who are correct 96 per cent of the time – it suggests that AI could soon be used to speed up and improve cancer screening.



Scientists have used machine learning to create an artificial intelligence system capable of

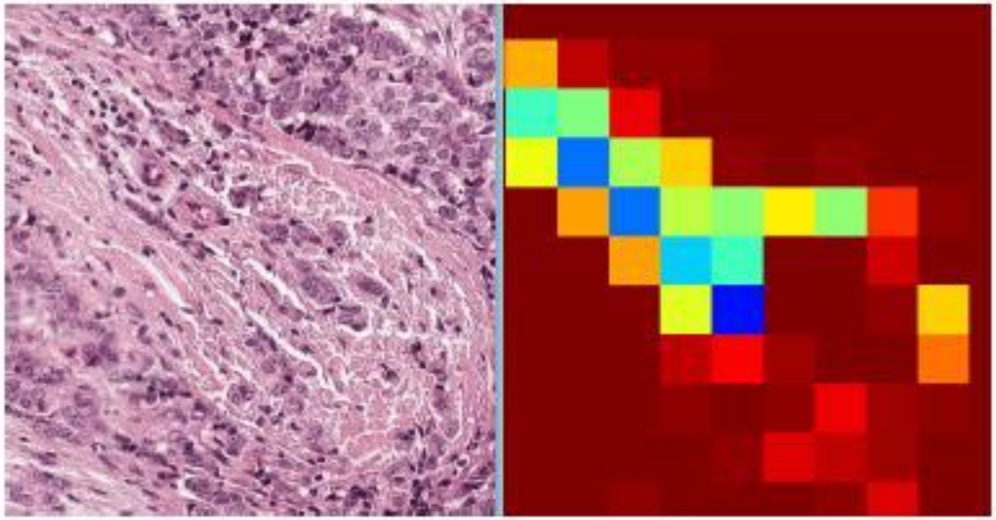


Fig. 5. **Left**: a patch from a H&E-stained slide. The darker regions are tumor, but not the lighter pink regions. **Right**: the corresponding predicted heatmap that accurately identifies the tumor cells while assigning lower probabilities to the non-tumor regions.

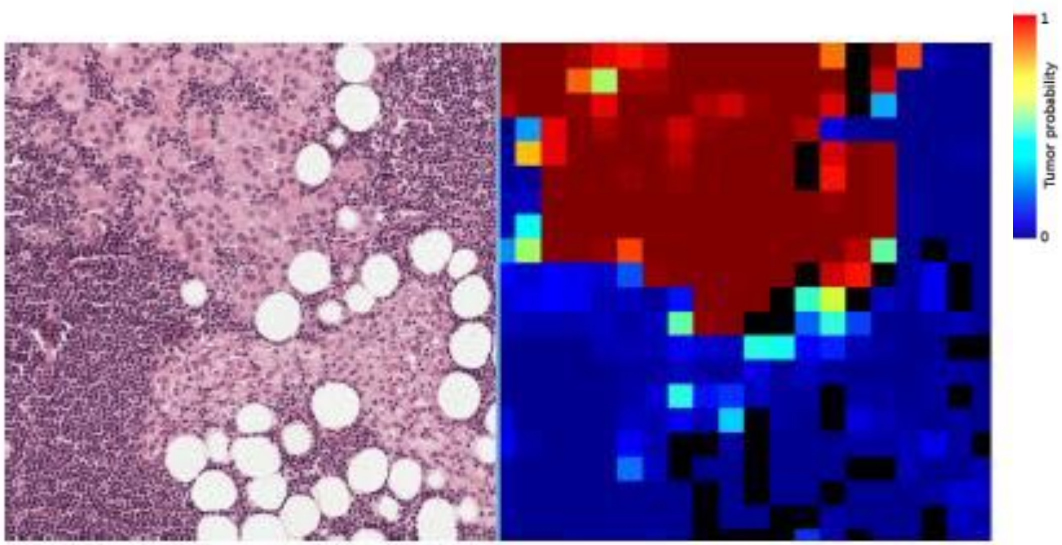


Fig. 6. **Left**: a patch from a H&E-stained slide, "Normal" 086. The larger pink cells near the top are tumor, while the smaller pink cells at the bottom are macrophages, a normal cell. **Right**: the corresponding predicted heatmap that accurately identifies the tumor cells while ignoring the macrophages.

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Could computers diagnose cancer? Artificial intelligence shown to spot early signs of a tumour with 92 per cent accuracy

- Machine can sift millions of cells to spot just a handful of malignant ones
- AI algorithm was trained using slides of samples of patients lymph nodes
- Human pathologists can diagnose breast cancer with 96 per cent accuracy
- When the machine and human combined, accuracy went to 99.5 per cent

By RICHARD GRAY FOR MAILONLINE
PUBLISHED: 13:05, 20 June 2016 | UPDATED: 13:11, 20 June 2016

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Computers could soon be helping to diagnose cancer in patients with the help of artificial intelligence that has been trained to spots the early signs of the disease.

An AI machine capable of accurately diagnosing breast cancer 92 per cent of the time has been developed by researchers.

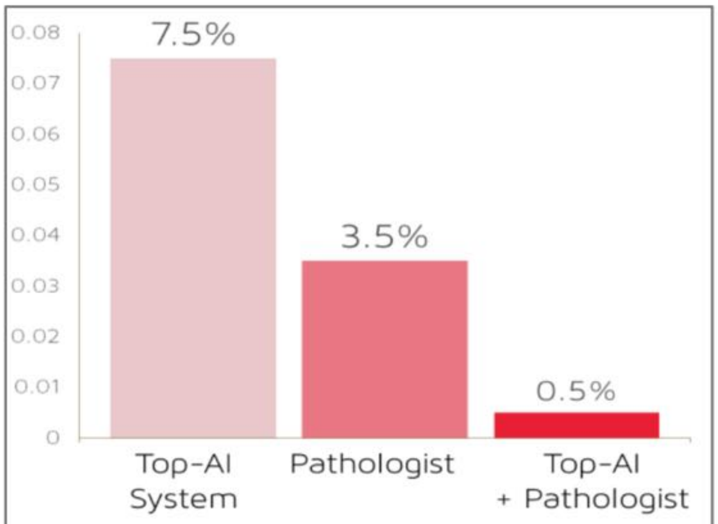
While it is still not quite as good as human specialists – who are correct 96 per cent of the time – it suggests that AI could soon be used to speed up and improve cancer screening.

Scientists have used machine learning to create an artificial intelligence system capable of

The White House ~~Takes~~ Took Note

ARTIFICIAL INTELLIGENCE FOR COMPUTATIONAL PATHOLOGY

Image interpretation plays a central role in the pathologic diagnosis of cancer. Since the late 19th century, the primary tool used by pathologists to make definitive cancer diagnoses is the microscope. Pathologists diagnose cancer by manually examining stained sections of cancer tissues to determine the cancer subtype. Pathologic diagnosis using conventional methods is labor-

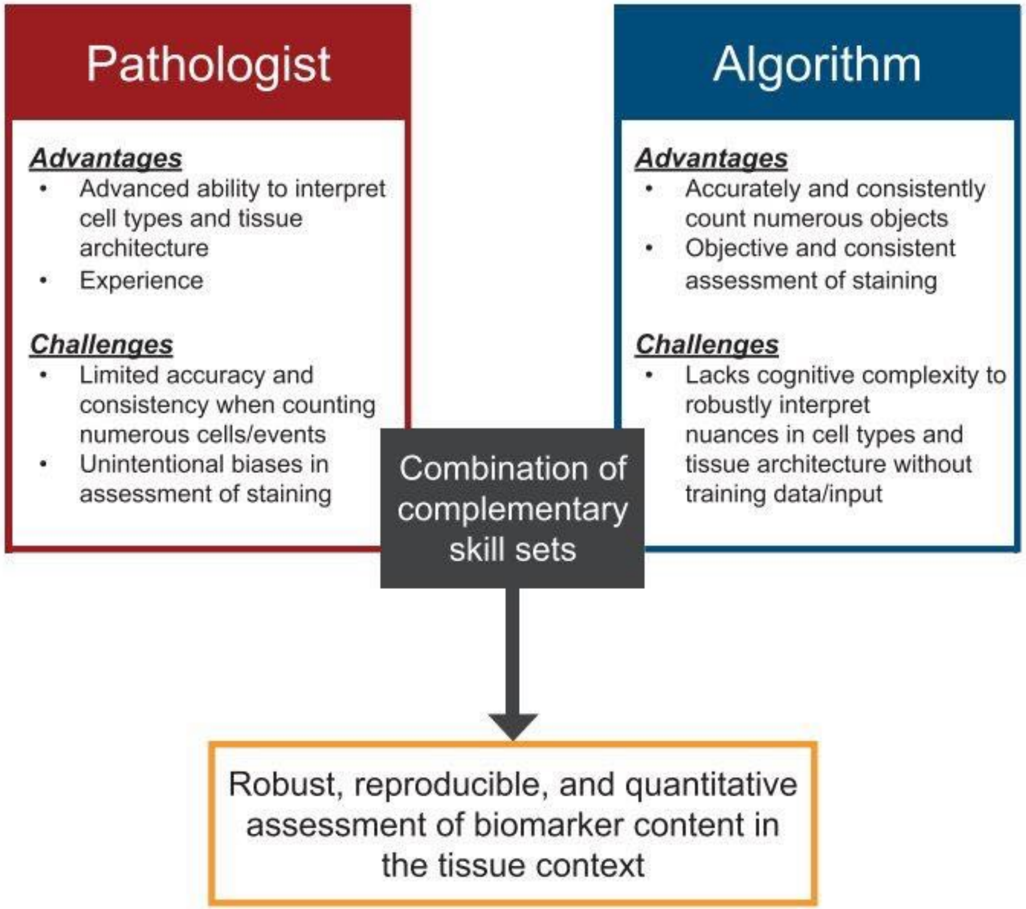


AI significantly reduces pathologist error rate in the identification of metastatic breast cancer from sentinel lymph node biopsies.

THE NATIONAL ARTIFICIAL INTELLIGENCE RESEARCH AND DEVELOPMENT STRATEGIC PLAN

October 2016

Pathologist + Algorithm



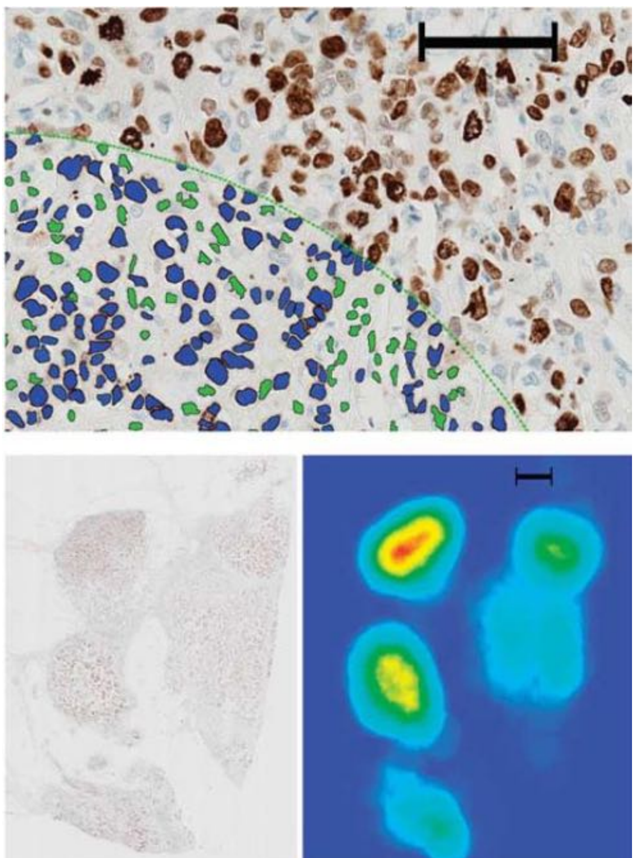
Aeffner *et al*., Arch Path Lab Med (Sep 2017)

Digital image analysis outperforms manual biomarker assessment in breast cancer

Modern Pathology (2016) 29, 318–329

Gustav Stålhammar[1,2], Nelson Fuentes Martinez[1,3], Michael Lippert[4], Nicholas P Tobin[5], Ida Mølholm[4,6], Lorand Kis[7], Gustaf Rosin[1], Mattias Rantalainen[8], Lars Pedersen[4], Jonas Bergh[1,5,9], Michael Grunkin[4] and Johan Hartman[1,5,7]

[1]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [2]St Erik Eye Hospital, Stockholm, Sweden; [3]Södersjukhuset, Stockholm, Sweden; [4]Visiopharm A/S, Hoersholm, Denmark; [5]Cancer Center Karolinska, Stockholm, Sweden; [6]Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kongens Lyngby, Denmark; [7]Department of Clinical Pathology, Karolinska University Hospital, Stockholm, Sweden; [8]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden and [9]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden



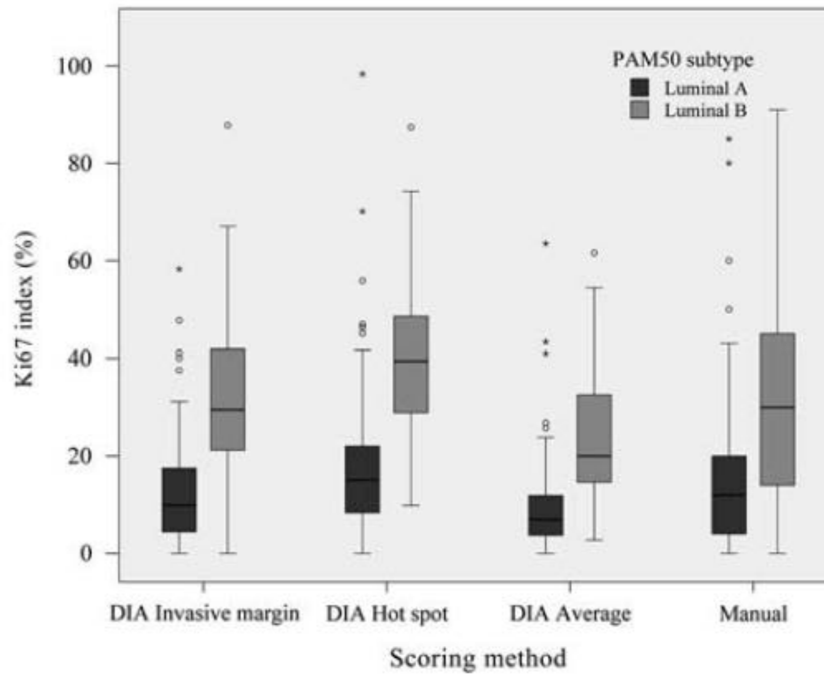


Figure 2 Clustered box plot for Ki67 index (%) by each scoring method in PAM50 Luminal A and B subtypes. Error bars represent 95% confidence interval. Circles represent outliers and asterisks represent extremes. DIA, digital image analysis ($n = 214$).

Digital image analysis outperforms manual biomarker assessment in breast cancer

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Ki67 scoring method	*Sensitivity for PAM50 Luminal B vs A*	*Specificity for PAM50 Luminal B vs A*	*Proportion misclassified*
DIA invasive margin			
Cutoff ≥ 20%	84%	78%	20%
Cutoff ≥ 20.2% *	82%	79%	20%
DIA hot spot			
Cutoff ≥ 20%	90%	65%	24%
Cutoff ≥ 25.2% *	86%	77%	19%
DIA average			
Cutoff ≥ 20%	60%	90%	31%
Cutoff ≥ 15.5% *	80%	83%	19%
Manual			
Cutoff ≥ 20%	75%	70%	30%
Cutoff ≥ 22.5% *	74%	75%	29%

Manual scores retrieved from patient records.
* = Adjusted cutoffs.

Detection of uNK+Stromal Cells

- Ratio of uNK to stromal cells is a good indicator of recurrent miscarriages
- Women with high numbers of uNK cells are more likely to have a live birth if given glucocorticoids in lieu of placebo
- Endometrial biopsy slides stained with Hematoxylin and DAB for CD56 to label the uterine Natural Killer (uNK) cells

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Health

'Crucial' new recurrent miscarriage insight

By James Gallagher
Health and science reporter, BBC News

12 September 2013 | Health

Fertility scientists say they have made a "crucial breakthrough" in understanding why some women have repeated miscarriages.

There has been debate about whether giving steroids would help women who have lost multiple pregnancies.

University of Warwick researchers say they have now shown how low steroid levels lead to some miscarriages.

More than one in seven pregnancies end in miscarriage.

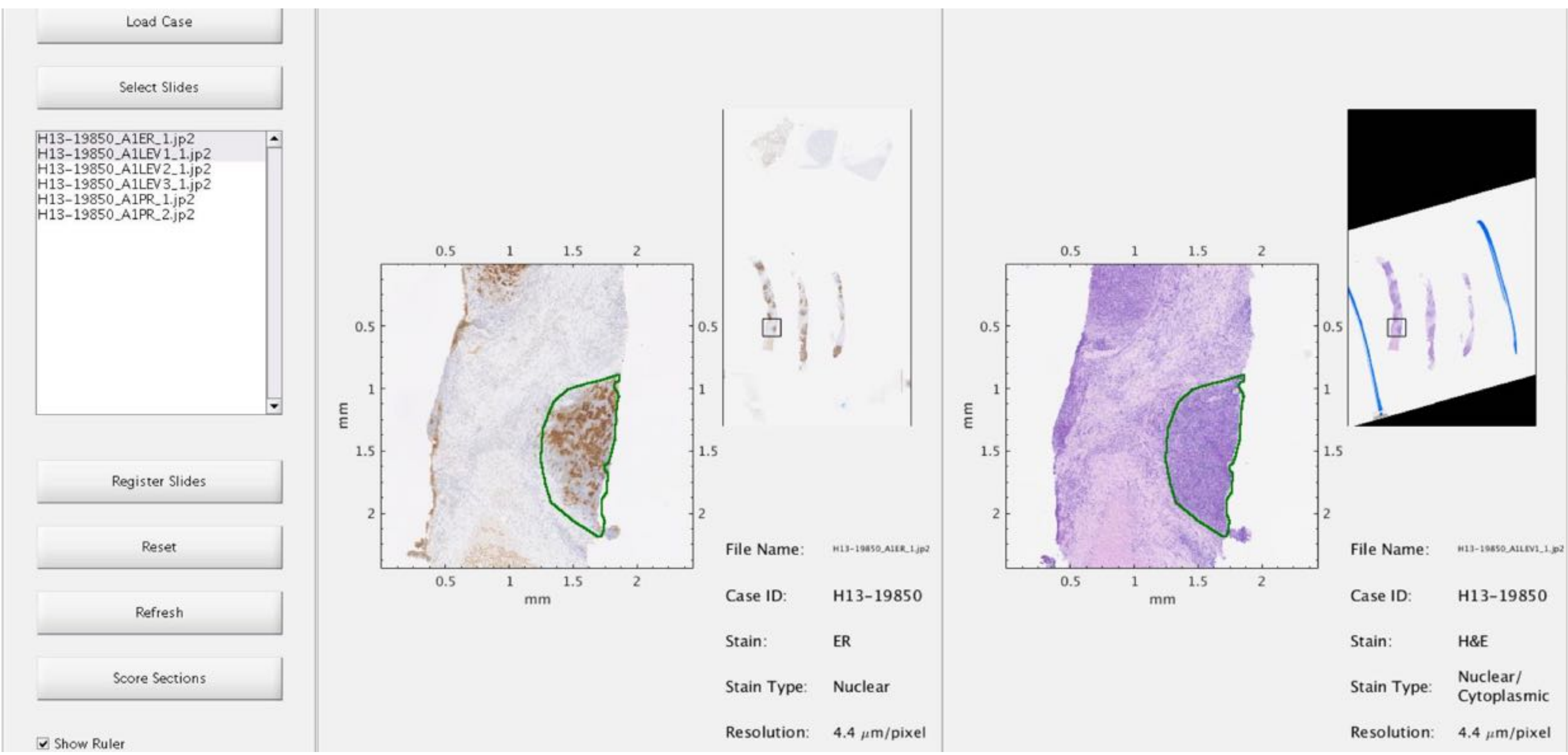
Quenby et al., *J Clin End Met* 2013

Automated ER & PR scoring

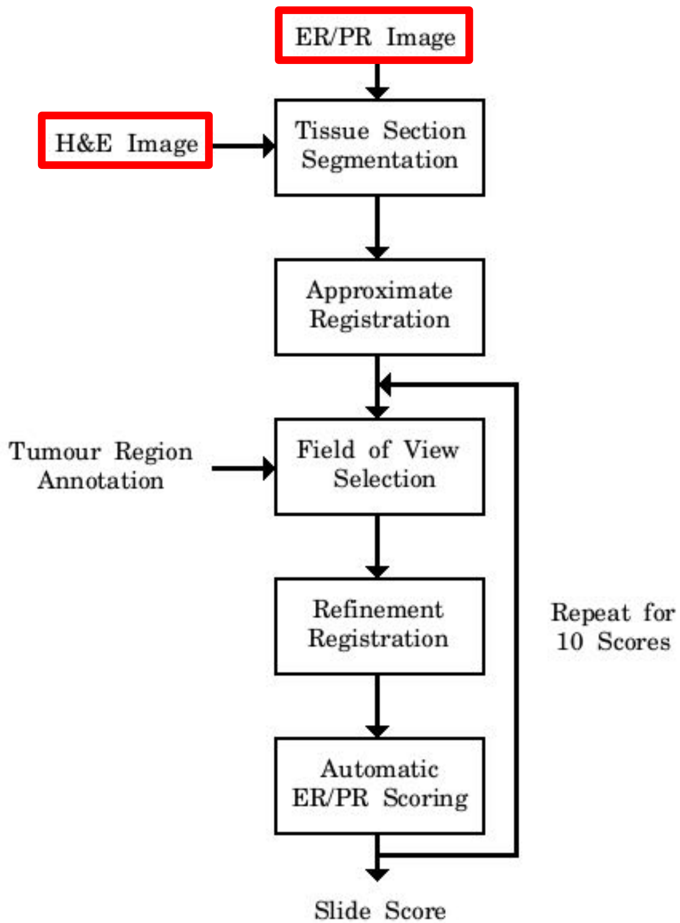
Simultaneous Automatic Scoring of Hormone Receptors in Tumour Areas in Whole Slide Images of Breast Cancer Tissue Slides

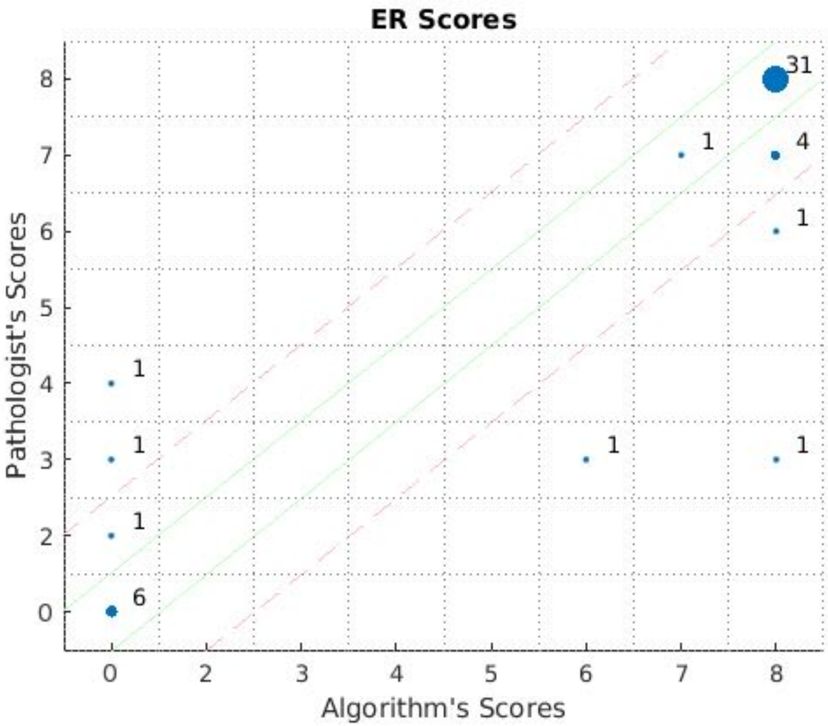
Nicholas Trahearn[a], Yee Wah Tsang[b,c], Ian Cree[c], David Snead[b,c], Nasir Rajpoot[a]

[a] Department of Computer Science, University of Warwick, United Kingdom
[b] Department of Pathology & [c] Centre of Excellence for Digital Pathology, University Hospitals Coventry and Warwickshire, United Kingdom



Multi-IHC Analyser




ER Scores
Pathologist's Scores
Algorithm's Scores
0
2
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31
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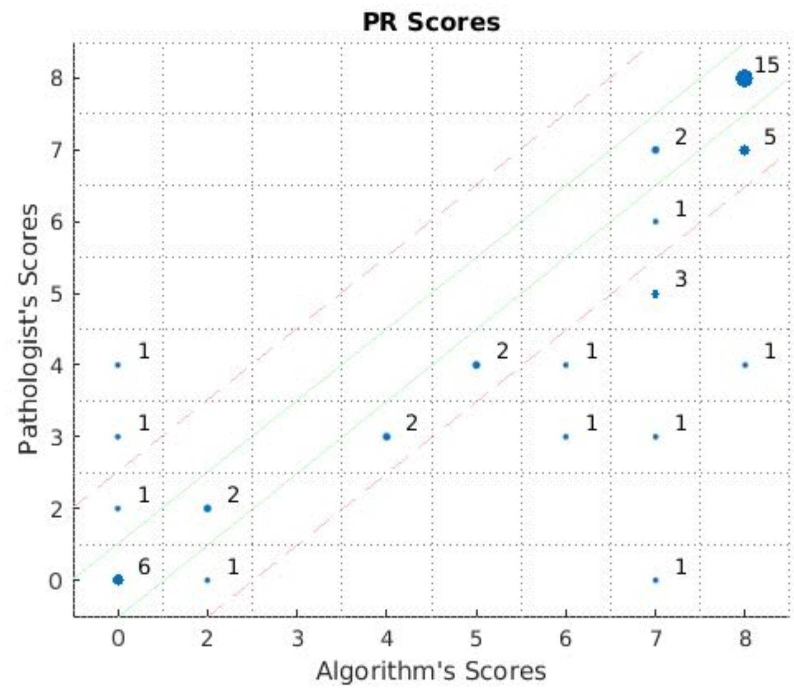
6


PR Scores
Pathologist's Scores
Algorithm's Scores
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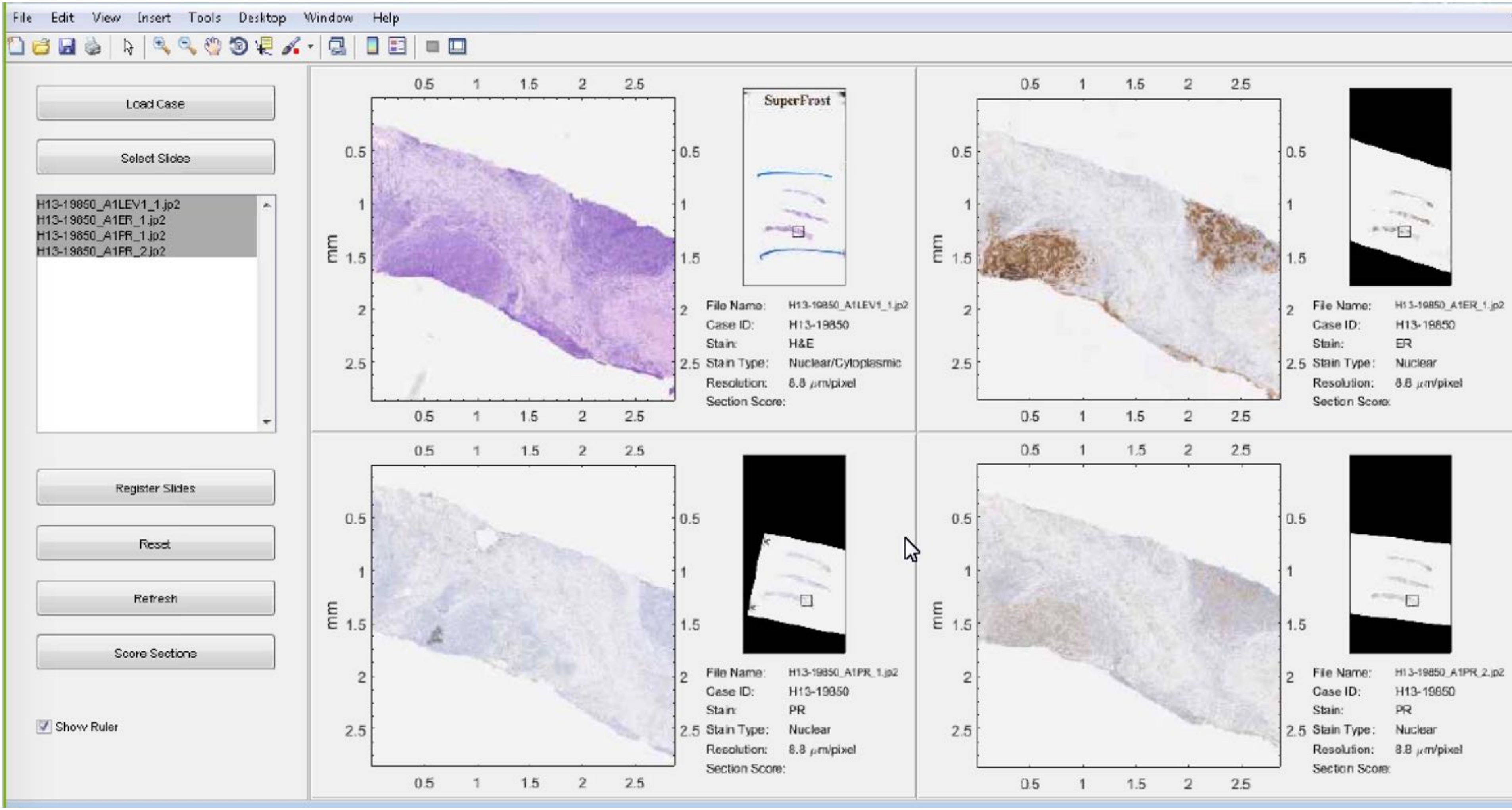
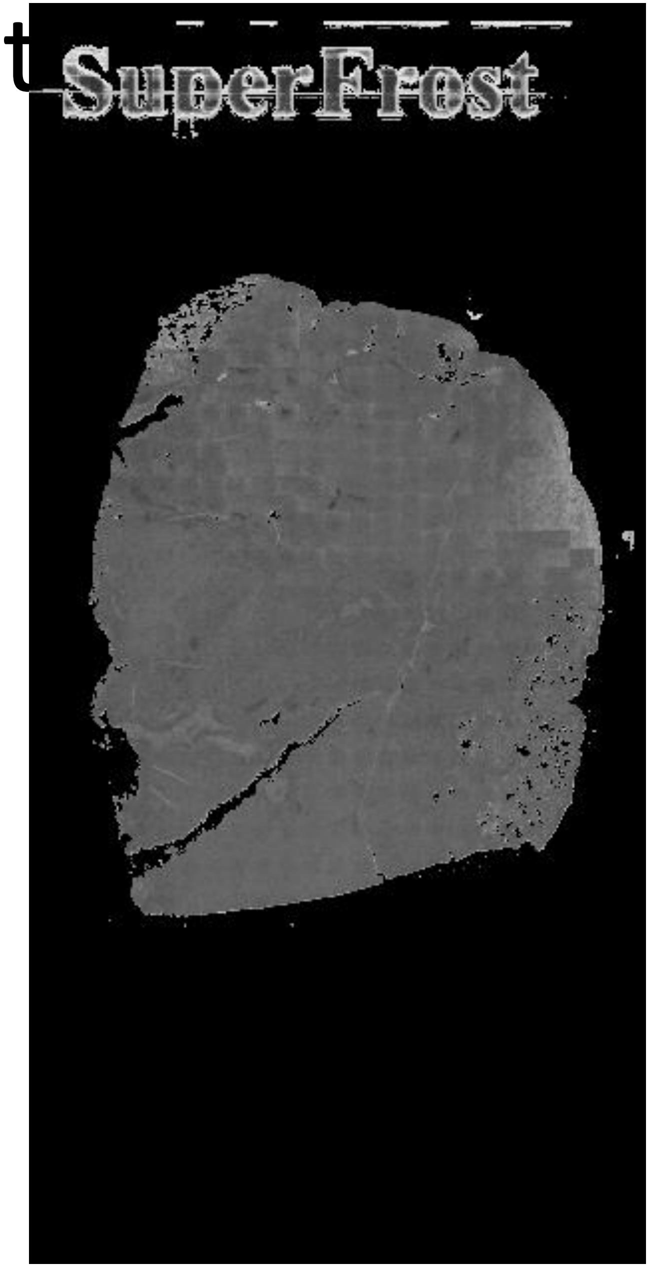
Multi-IHC Analyser

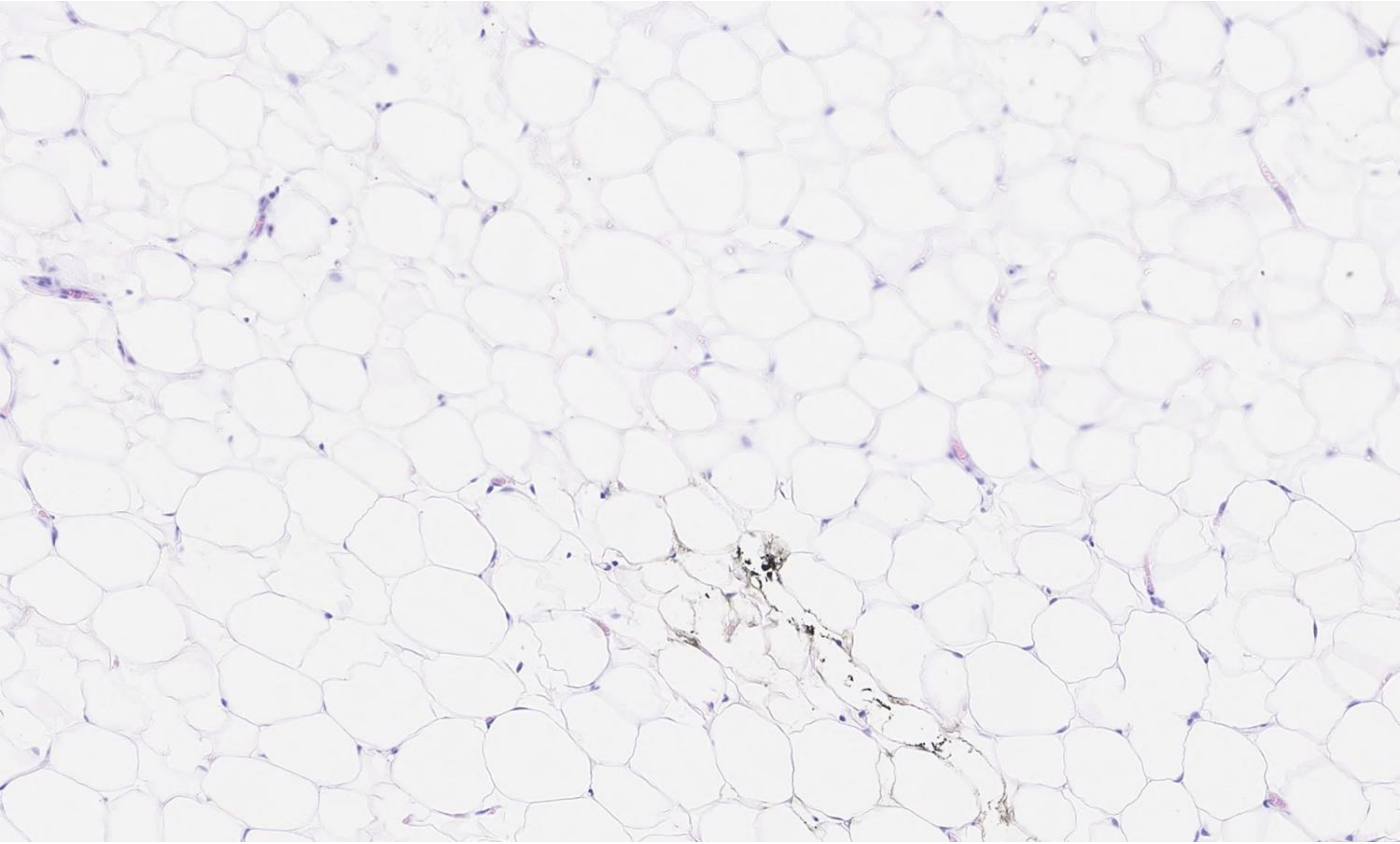


Trahearn, Rajpoot *et al.*, *submitted*

Blur report t

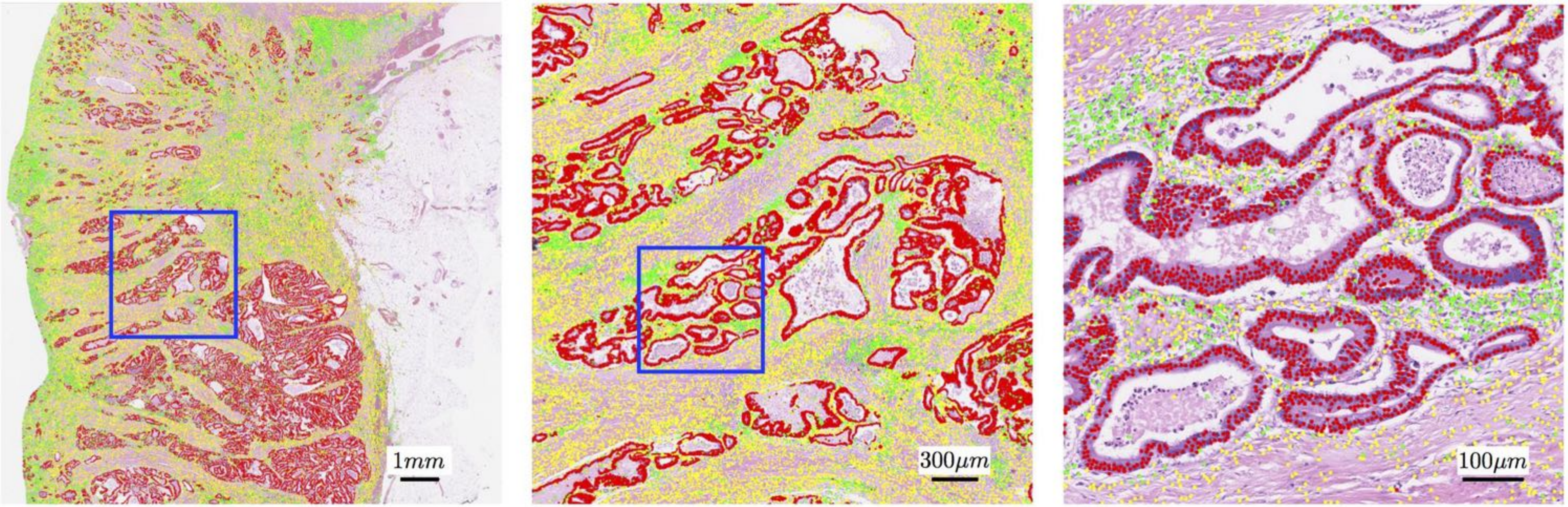
92	122	199	213
189	212	32	47
141	158	33	47
335	345	38	54
251	264	34	47
164	182	36	46
259	276	25	46
304	313	492	506
86	94	34	47
220	232	25	33





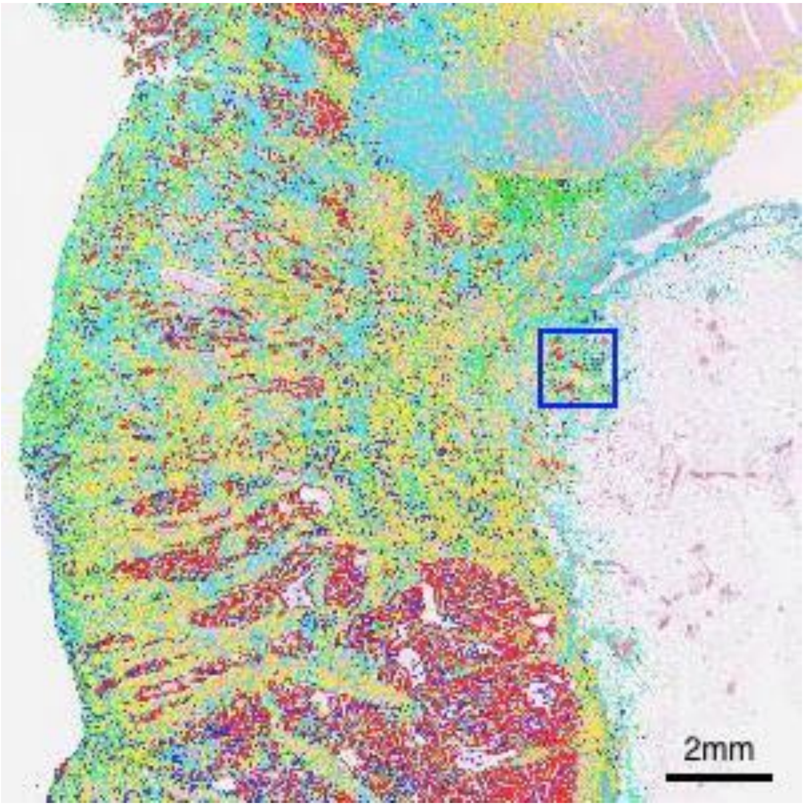
Deep Learning - Profiling Tumour Microenvironment

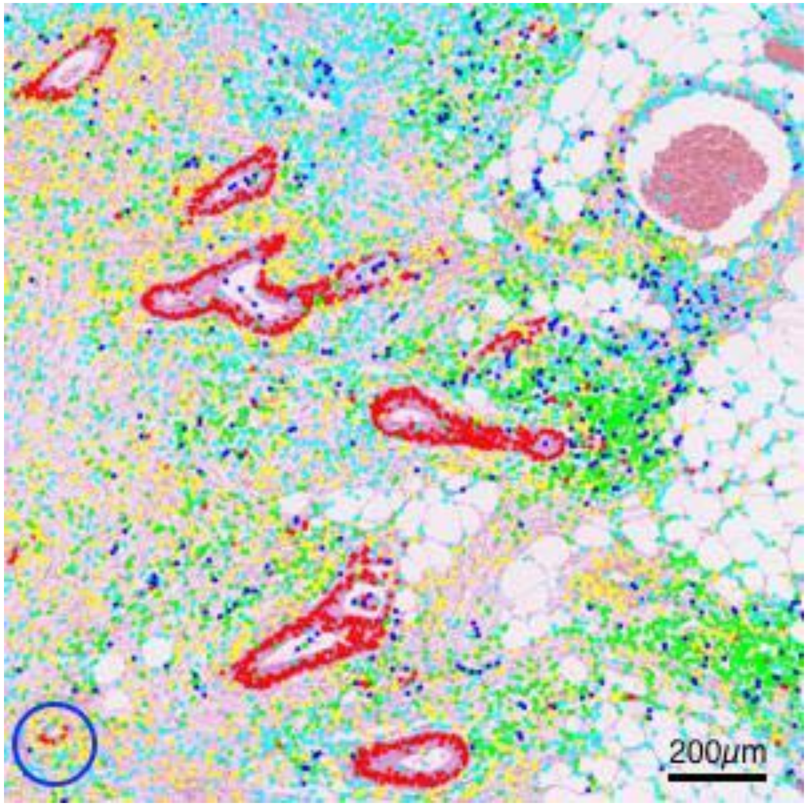
- Cell recognition in large sets of whole-slide images
- Analytics for profiling the tumor micro-environment



Sirinukunwattana *et al*., ***IEEE Trans Medical Imaging*** special issue on ***Deep Learning in Medical Imaging*** (May 2016)

Invasive Tumour Fronts





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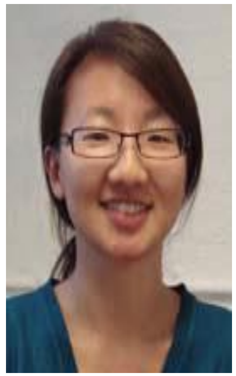

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