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Digital pathology and pathology informatics

Kyoungbun Lee, MD
Department of Pathology, Seoul National University Hospital

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Disclosure

- I have no conflict of interest

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Outline

- **Introduction of digital pathology**
- **Digital pathology for primary diagnosis**
  Component of digital pathology system for primary diagnosis
  Digital pathology workflow, SNUH
  Issues in implementation of digital pathology system
- **Digital pathology for research**
  Computational pathology : quantification, discrimination, prediction
  Reconstruction
- **New technique for digital pathology**
  Slide-free non-destructive pathology

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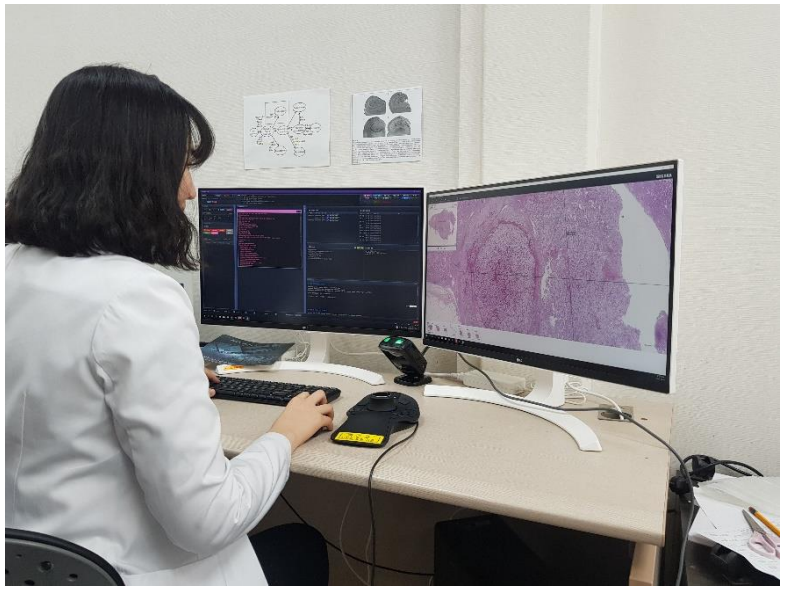
What is digital pathology?

- ***Wikipedia [https://en.wikipedia.org/wiki/Digital_pathology]***

image-based information environment which is enabled by **computer technology** that allows for the management of information generated from a **digital slide**. Digital pathology is enabled in part by **virtual microscopy**, which is the practice of **converting glass slides into digital slides** that can be viewed, managed, shared and analyzed **on a computer monitor**. With the advent of Whole-Slide Imaging, the field of digital pathology has exploded and is currently regarded as one of the most promising avenues of diagnostic medicine in order to achieve even better, faster and cheaper diagnosis, prognosis and prediction of cancer and other important disease



What can we do with digital pathology?

JS Song, Korean medical education 2006.
Pantanowitz L. Journal of pathology informatics 2010
J Oral Maxillofac Pathol 2016;20: 284-288

- ***What can we do with glass slide?***

Education

Fig. 1. Computer laboratory for practical class using virtual microscopes.

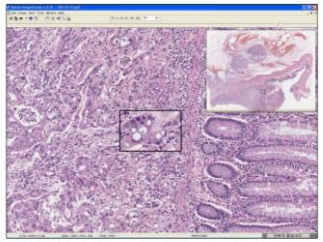


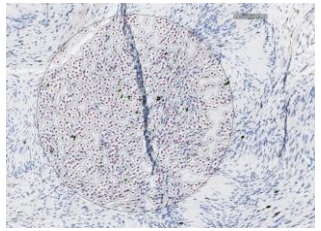
Fig. 2. Screenshot of the virtual microscope. The ImageScope viewer shows a histopathologic lesion of the thumbnail at the right upper corner and the magnifier at the center.

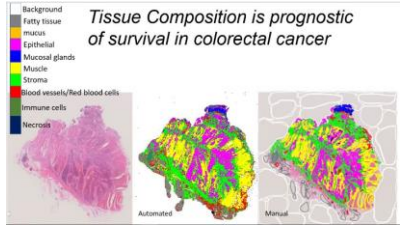
Figure 3: Whole slide images help create a "virtual multiheaded microscope" that supports interactive education (Image courtesy of BioImagene)

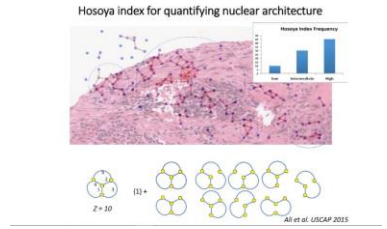
Research & bioindustry

Prognosis factor
Classification
Biomarker development
Toxicology
Drug development
: semi-quantitative grading
consensus meeting

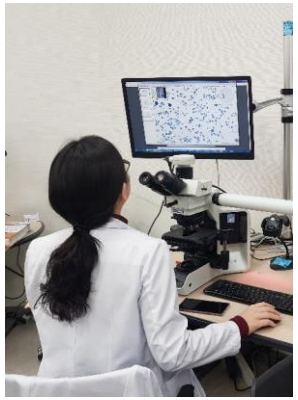
Segmentation, quantification, computation, prediction

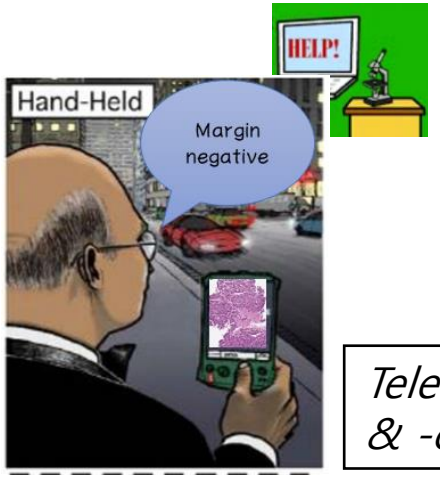






Primary diagnosis





Teleconference & -consult

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  - Component of digital pathology system for primary diagnosis
  - Digital pathology workflow, SNUH
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  - Computational pathology : quantification, discrimination, prediction
  - Reconstruction
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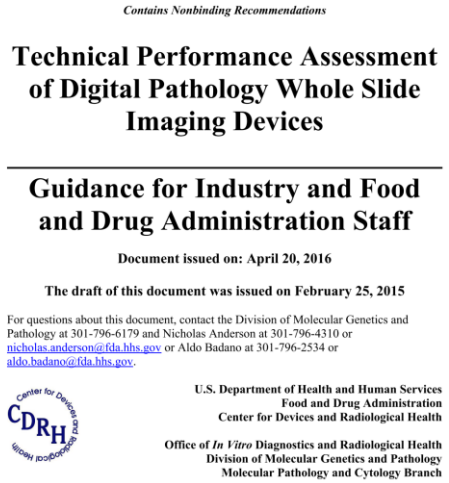
Regulation of whole slide image for primary diagnosis

- US

  Philips IntelliSite Pathology Solutions for primary pathology diagnosis

  : 2000 surgical pathology cases (15,925 readings) : optical interpretation rate difference of 0.4% with a 95% confidence interval (−0.3–1.0) indicating noninferiority for digital versus optical reads



Contains Nonbinding Recommendations

Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: April 20, 2016

The draft of this document was issued on February 25, 2015

For questions about this document, contact the Division of Molecular Genetics and Pathology at 301-796-6179 and Nicholas Anderson at 301-796-4310 or nicholas.anderson@fda.hhs.gov or Aldo Badano at 301-796-2534 or aldo.badano@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of *In Vitro* Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Molecular Pathology and Cytology Branch

Stony Brook University

FDA News Release

FDA allows marketing of first whole slide imaging system for digital pathology

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release April 12, 2017

Release The U.S. Food and Drug Administration today permitted marketing of the Philips IntelliSite Pathology Solution (PIPS), the first whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI system for these purposes.

Korea's Drug Ministry approves Philips digital pathology solution

By Sohn Ji-young

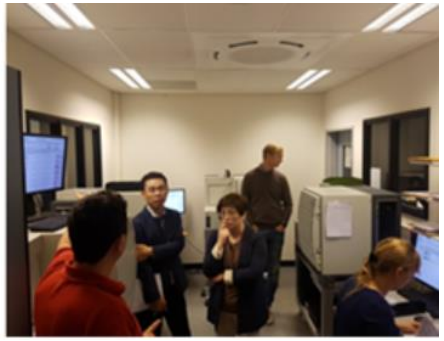
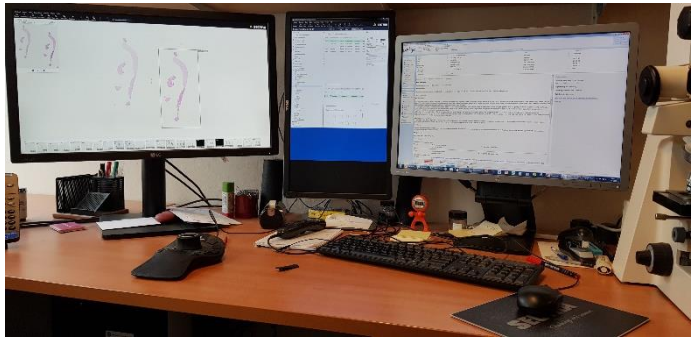
Published : Jul 10, 2018 - 16:08 Updated : Jul 10, 2018 - 16:08

Philips Korea announced Tuesday that South Korea's Ministry of Food and Drug Safety has approved its digital pathology solution, the Philips IntelliSite Pathology Solution, for diagnostic use in the country.

Pathologists in Korea can now use the digital pathology technology from Philips to assess and diagnose clinical histology cases digitally, instead of with a microscope, with the aim to enhance laboratory efficiency and quality, the firm said.

Fully digitalized pathology lab.

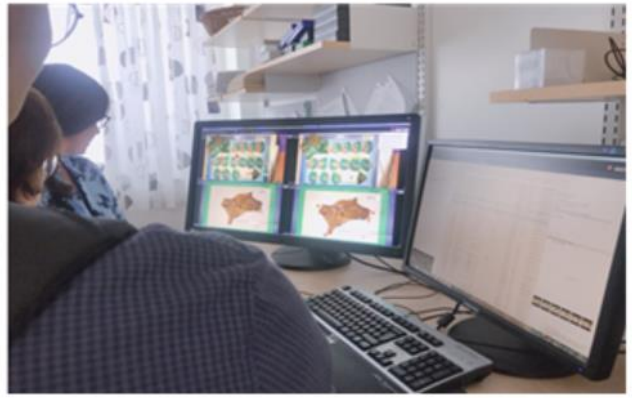
2018, 8.17, University Medical Center Utrecht, Netherland, Amsterdam

> 1,000 beds, >10,000 employes
20,000 /yr histopathology requests
156,000 slides/yr
15 pathologists , 10 residents

➔ *6 scanner running*

2018.8.16, Linkoping University Hospital, Linkoping, Sweden



30,000/yr histopathology requests
180,000 slides/yr

20 pathologists

➔ *27 digital work stations*
> 1,000,000 slides 440TB
Start in 2010, full digital in 2017

Components of digital pathology

- Slide scanner : image acquisition
- Image management : data, messages, integration in LIS
- Viewer software and image storage system
- Image evaluation and analysis system
- Hardware of users : user workstation and viewing monitor

Implementation of digital pathology & workflow, SNUH

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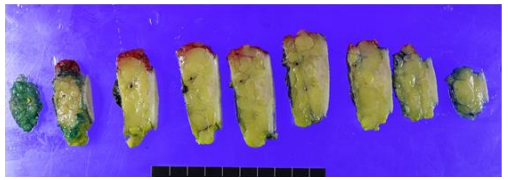
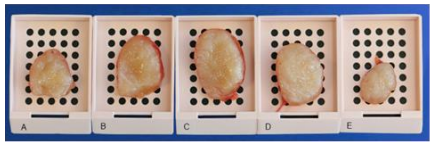
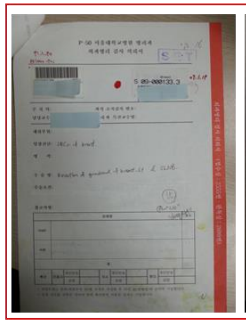
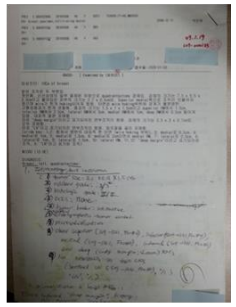
Change of pathology workflow

Submit → Gross (dictate) → Glass slide → reading → Reporting (paper/typist) → Slide repository → Space, time, man-power









Laboratory (hospital) information system

Digital pathology system

1st step : Traditional paper-based work-flow ➔ paper-less workflow

Pathology PACS and HIS system: SNUH

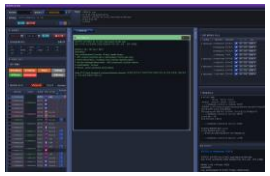
Digital Gross Photography system

Sequencer PCR

FISH/IF/EM images

Slide scanner

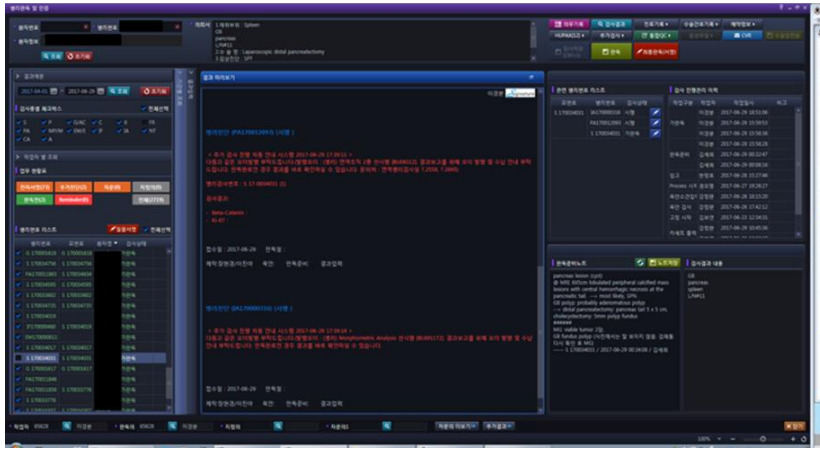
HIS system, upgrade 2016



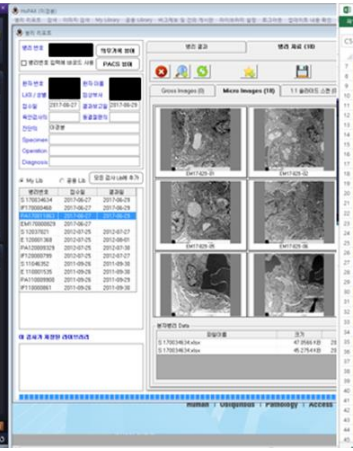
Order
Patient information
Paper-less pathology report
Lab work-flow management
Slide tracking system

Pathology image server
(HUPAX, 2009, SNUH&Humintec)

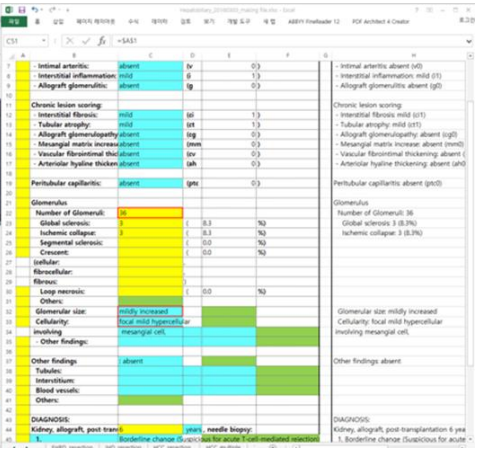
Hospital Information System



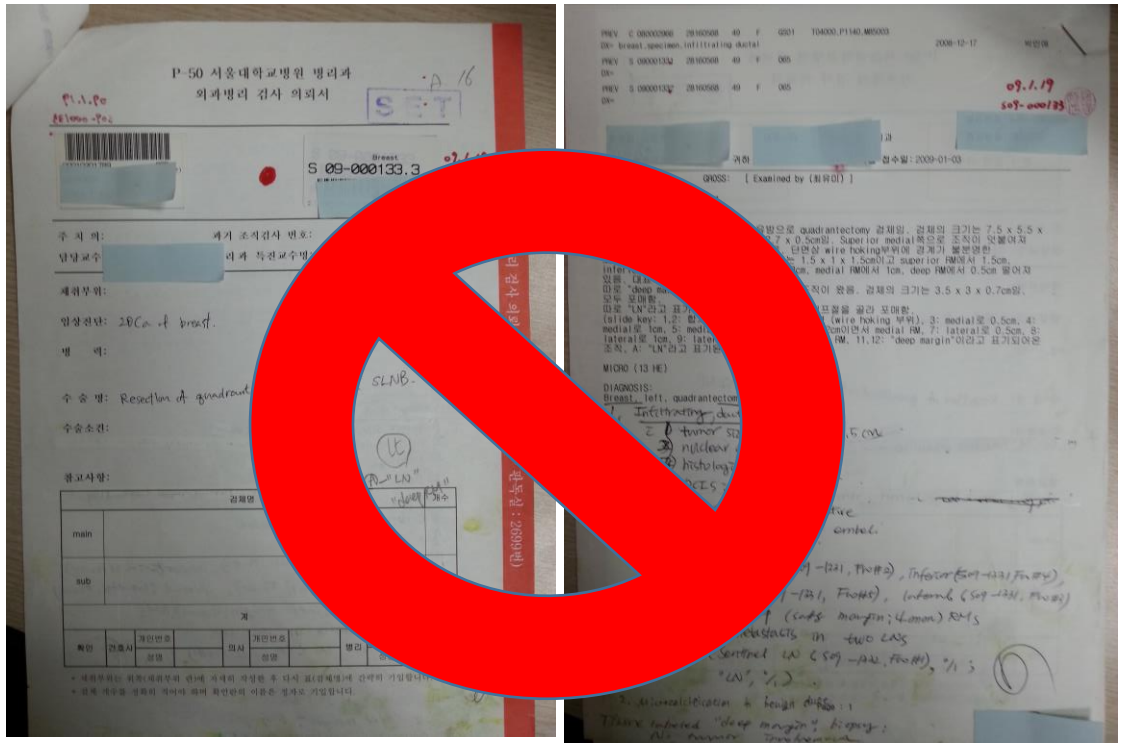
Pathology PACS



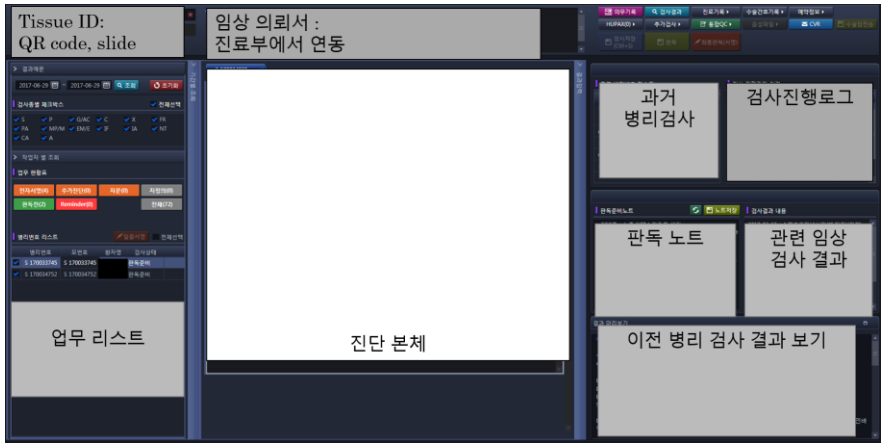
Template



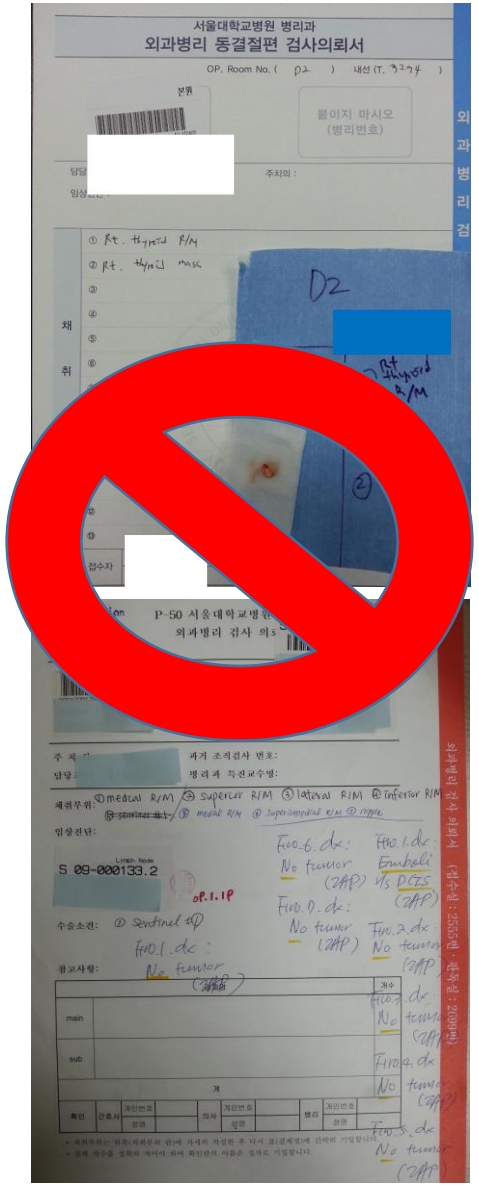
HIS: main report



1. Order ancillary test
2. QA & QC
3. Statistics

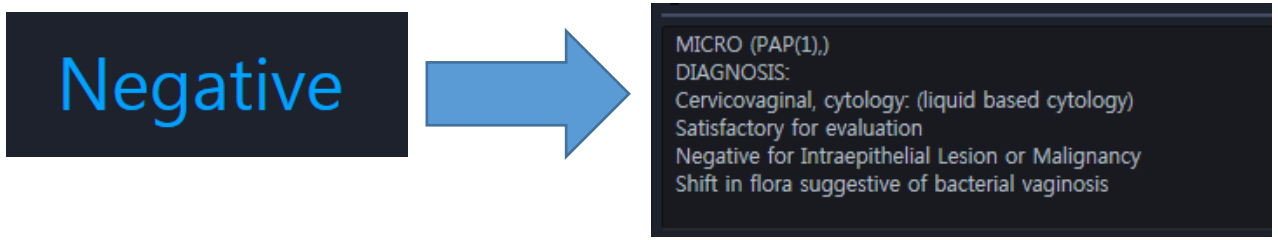


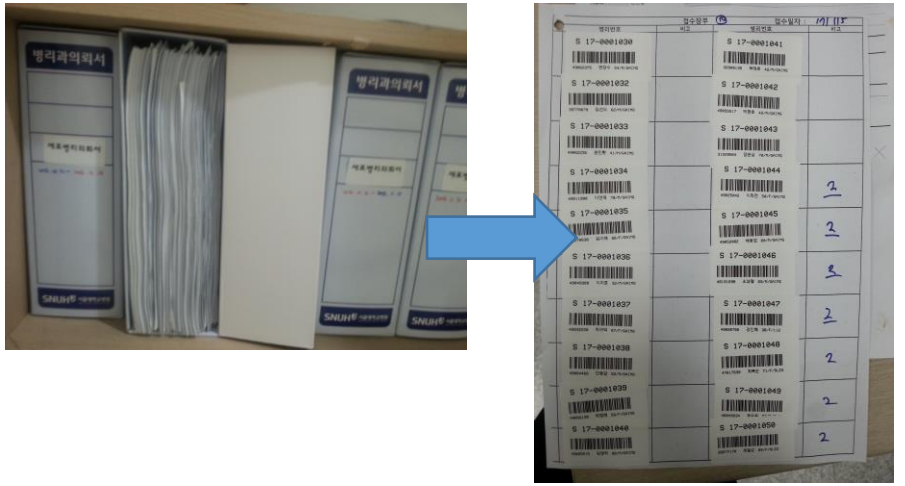
HIS: Frozen report



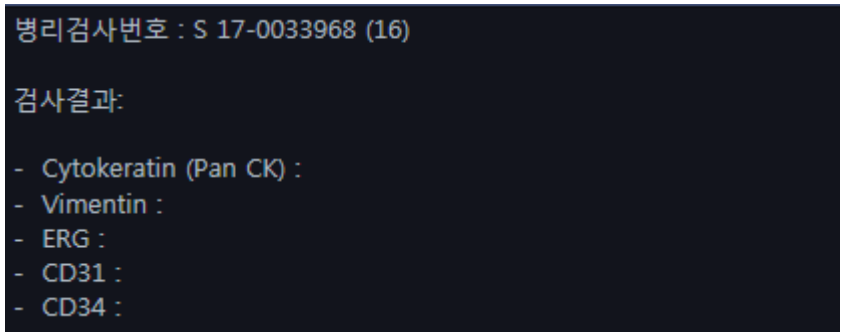
HIS: Automatic text loading

1. Cytology > Heading, screening result





2. Immunohistochemistry / special study> antibody item



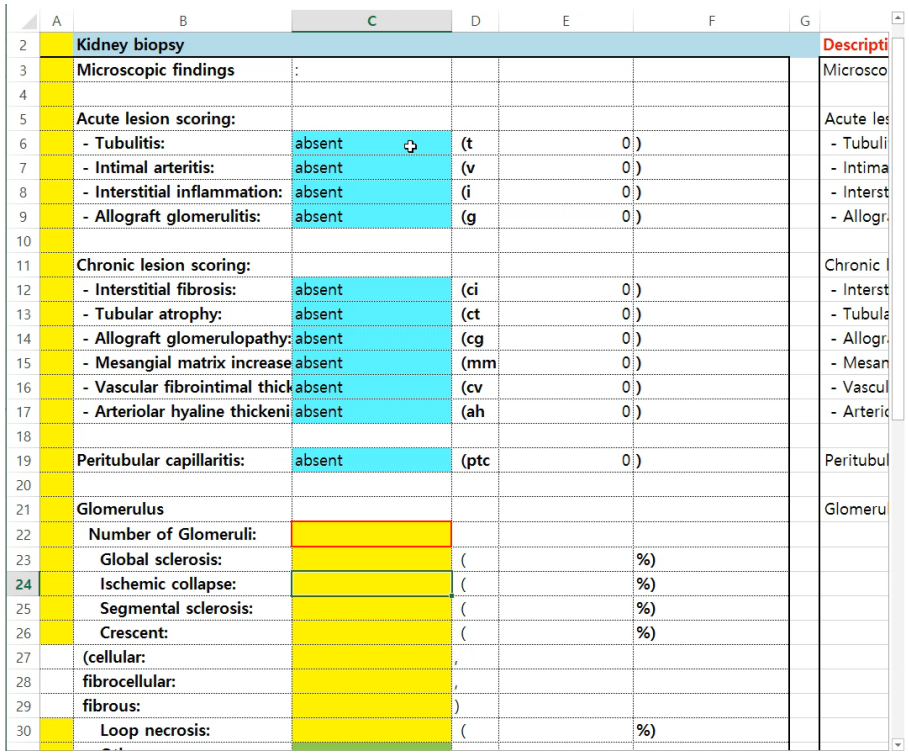
3. Gross examination, small tissue > gross text & heading

Reporting template, SNUH

Check-list electronic file > Excel-based

Text join
Copy & paste

Text report : semi-structured text



	A	B	C	D	E	F	G	
2		Kidney biopsy						Descripti
3		Microscopic findings	:					Microsco
4								
5		Acute lesion scoring:						Acute les
6		- Tubulitis:	absent	(t	0	)		- Tubuli
7		- Intimal arteritis:	absent	(v	0	)		- Intima
8		- Interstitial inflammation:	absent	(i	0	)		- Interst
9		- Allograft glomerulitis:	absent	(g	0	)		- Allogr
10								
11		Chronic lesion scoring:						Chronic l
12		- Interstitial fibrosis:	absent	(ci	0	)		- Interst
13		- Tubular atrophy:	absent	(ct	0	)		- Tubula
14		- Allograft glomerulopathy:	absent	(cg	0	)		- Allogr
15		- Mesangial matrix increase	absent	(mm	0	)		- Mesan
16		- Vascular fibrointimal thick	absent	(cv	0	)		- Vascul
17		- Arteriolar hyaline thickeni	absent	(ah	0	)		- Arteric
18								
19		Peritubular capillaritis:	absent	(ptc	0	)		Peritubul
20								
21		Glomerulus						Glomeru
22		Number of Glomeruli:						
23		Global sclerosis:		(		%)		
24		Ischemic collapse:		(		%)		
25		Segmental sclerosis:		(		%)		
26		Crescent:		(		%)		
27		(cellular:		,				
28		fibrocellular:		,				
29		fibrous:		)				
30		Loop necrosis:		(		%)		

Microscopic findings:

Acute lesion scoring:
- Tubulitis: mild (t1)
- Intimal arteritis: absent (v0)
- Interstitial inflammation: mild (i1)
- Allograft glomerulitis: mild (g1)

Chronic lesion scoring:
- Interstitial fibrosis: mild (ci1)
- Tubular atrophy: mild (ct1)
- Allograft glomerulopathy: absent (cg0)
- Mesangial matrix increase: absent (mm0)
- Vascular fibrointimal thickening: mild (cv1)
- Arteriolar hyaline thickening: mild (ah1)

Peritubular capillaritis: mild (ptc1)

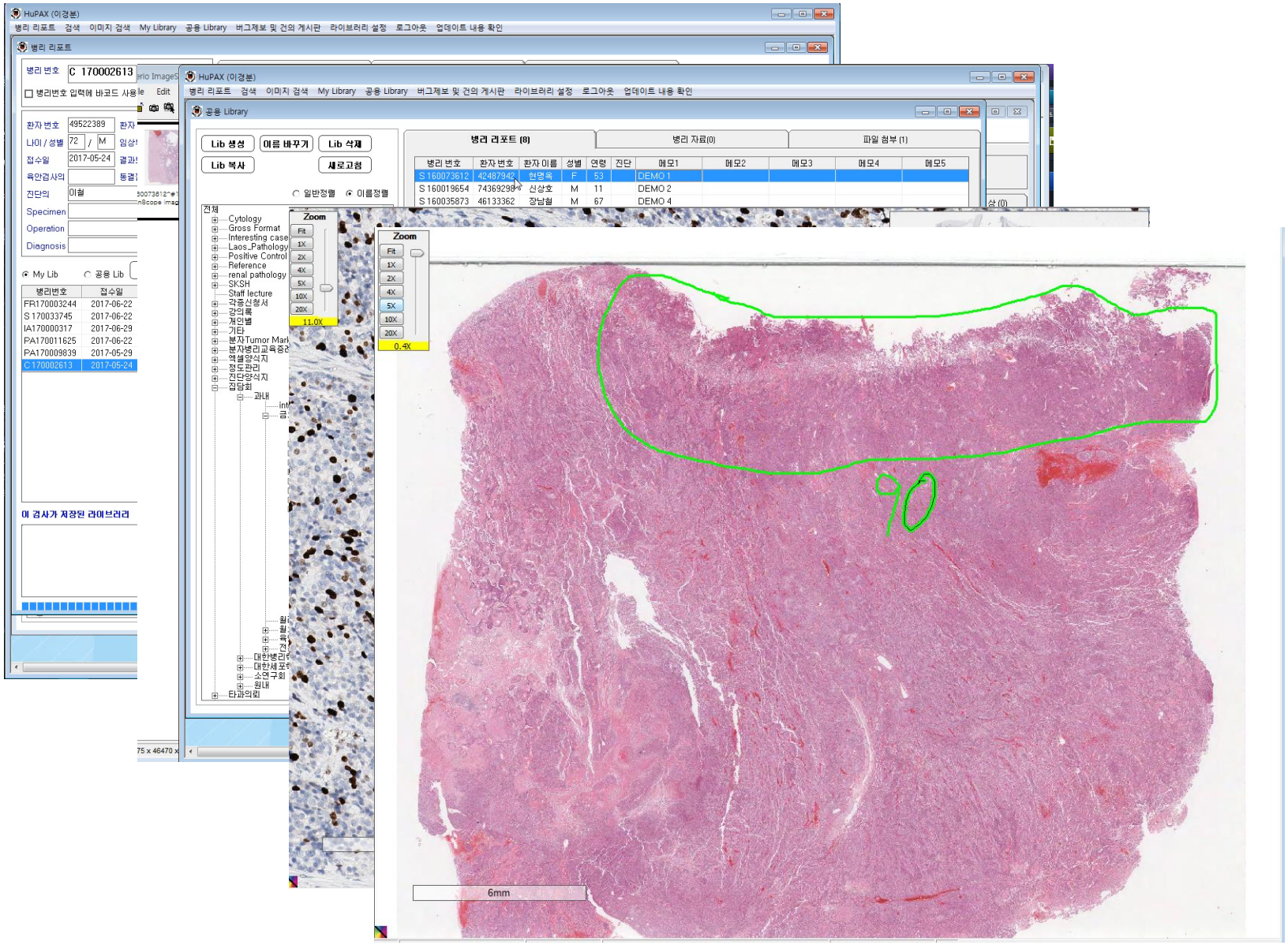
Glomerulus
Number of Glomeruli: 24
Global sclerosis: 8 (33.3%)
Glomerular size: mildly increased
Cellularity: normal
- Other findings: focal ischemic wrinkling,

Other findings: absent

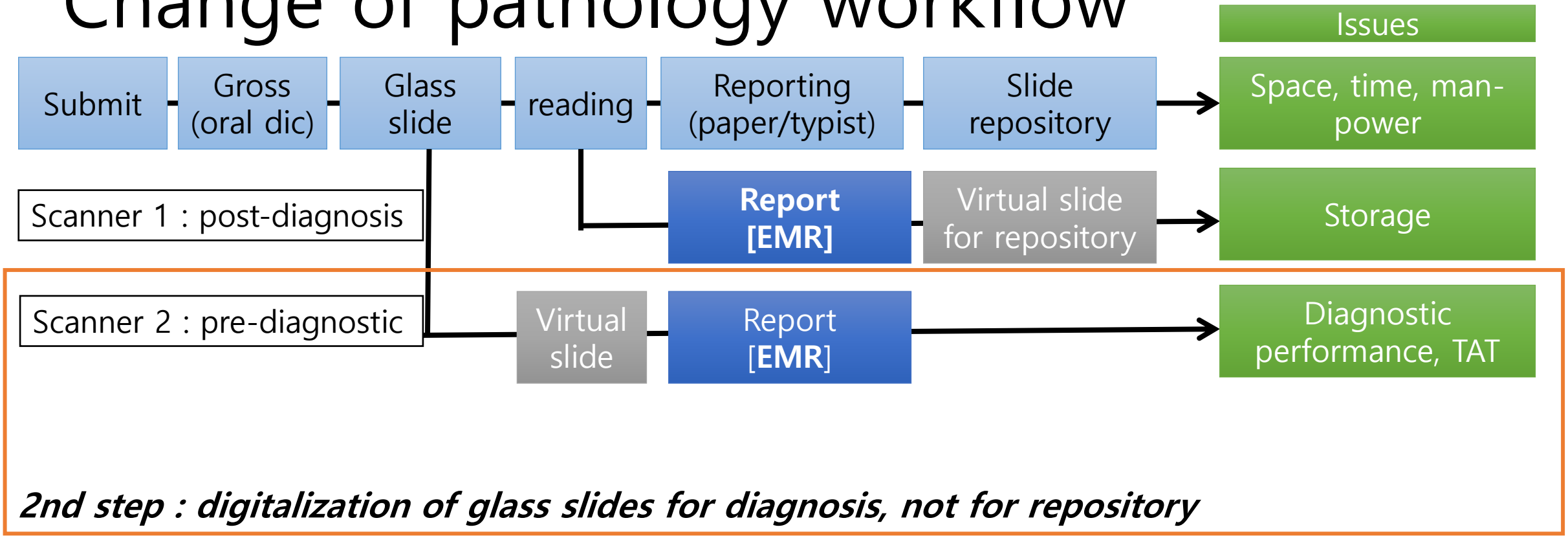
DIAGNOSIS:
Kidney, allograft, post-transplantation 6 years, needle biopsy:
1. Borderline change (Suspicious for acute T-cell-mediated rejection)
2. Interstitial fibrosis and tubular atrophy, grade I
(t1, v0, i1, g1 / ci1, ct1, cg0, mm0, cv1, ah1 / ptc1)

Pathology PACS: virtual slide

1. Previous slide review
2. Conference
3. Image analysis
4. Tumor marking
5. Research
6. Permanent storage



Change of pathology workflow



Digital pathology project: SNUH, 2017-2018

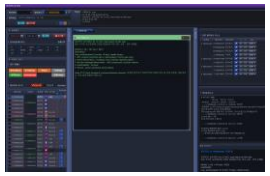
Digital Gross Photography system

Sequencer PCR

FISH/IF/EM images

Slide scanner x2

EMR system, 2016



Order
Patient information
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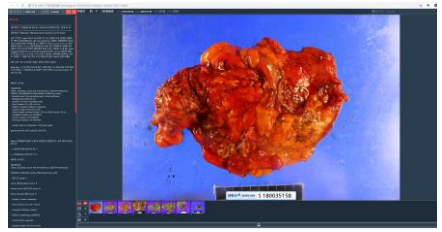
Slide tracking system

Pathology image server
(HUPAX, 2009년 개발, SNUH&Humintec)
HP ProLiant DL380p (Gen8)
Storage: 55Tb (18Tb, backup)

Server/storage

2 servers
55Tb>>220Tb

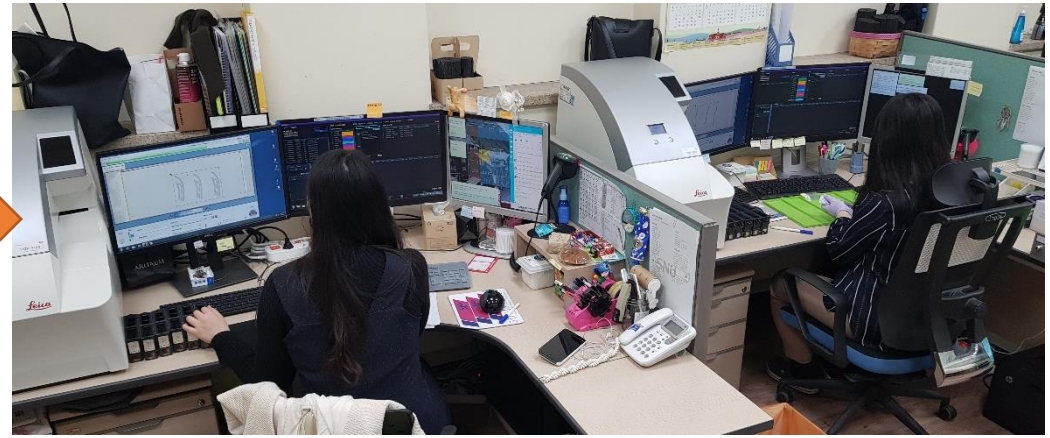


HUPAX upgrade & open to whole hospital

HUPAX web viewer

Pathologist workstation (2 sets)

Scanning



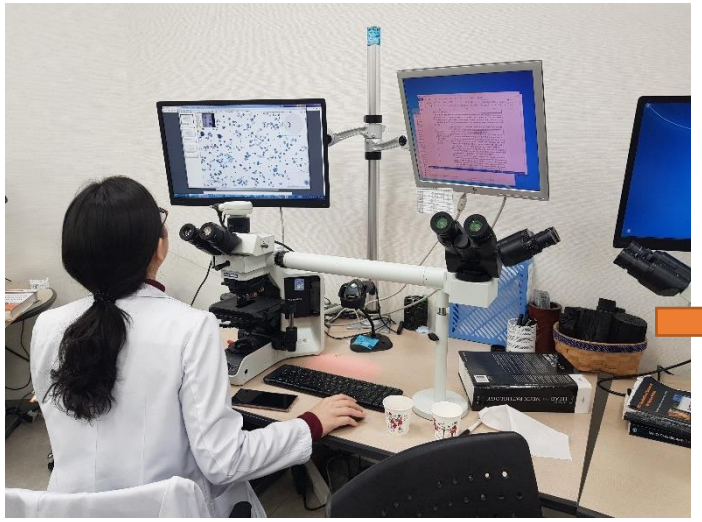
- ***Objects***
  post-diagnostic : selected glasser for conference, key slides for molecular test
  pre-diagnosis : image analysis, hepatobiliarypancreas, urology, medical kidney, bone and soft tissue, skin, CNS, pediatric cases

- ***Scan volume : File/data : 288,055 glass slides / 73Tb, 40% /total slides, 2018***

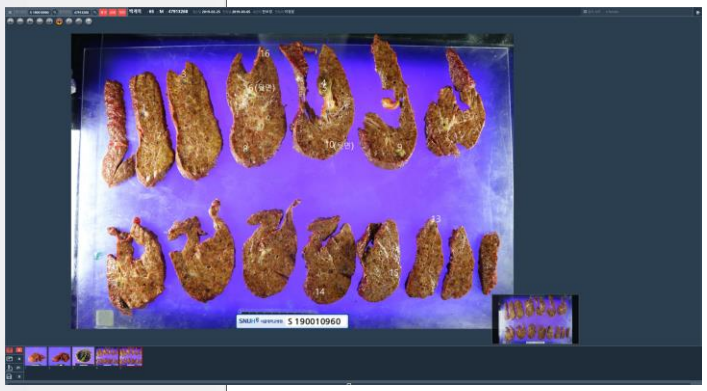
- ***Scan protocol and quality***
  cover slide mounting -> drying for 20min -> loading one rack (40 slides /rack)
  Rescan rates
  >5% **[SNUH 6.3% -> 2%]**
  stripe, focusing out
  histotechnical procedure : tissue fold, air bubbles, dirt on slides
  cannot find out tissue on autofocusing : limited tissue / too little, no positive stain
  automatic file loading to server by barcode system : no additional manual work for file management
  Slides can be seen within 1-3hr after loading

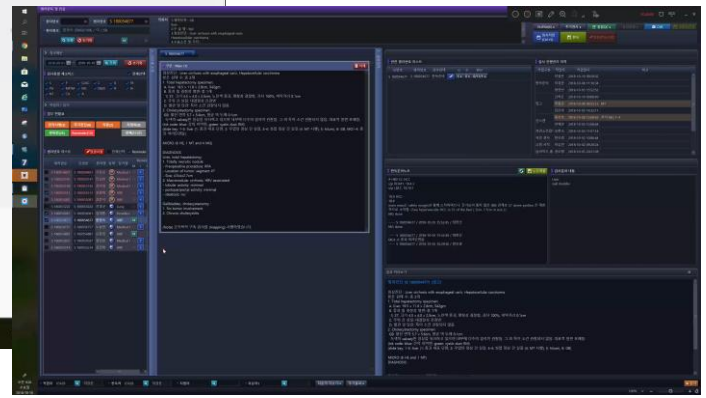
Pathology workstation

- *VS monitor : 4096x2160 resolution medical imaging display*
- *HIS monitor*
- *Secondary monitor for ancillary images*
  4096x2160 resolution medical imaging display
  HUPAX web viewer
- *3D mouse : navigation of vs*
- *PC : Intel i7-7700k, GTX1080, 8G RAM*



Primary diagnosis by WSI, SNUH





Diagnostic performance : SNUH

- Consecutive 235 건

장기	biopsy	operation	total
AOV	2		2
bile duct	6	1	7
bone	2	4	6
colon	74		74
duodenum	3		3
gallbladder		2	2
general		5	5
H&N	1		1
liver	13	7	20
LN	1		1
lung		2	2
medical kidney	12		12
ovary		2	2
pancreas	8	9	17
placenta	1	1	2
soft tissue	2	10	12
stomach	64	1	65
uterus ovary		2	2
총합계	189	46	235

- x20 / x40(medical kidney)
- Concordant rate : 91%

- Discordant rates : 9 % (20/235)

Activity	8
Dysplasia grade	1
H. pylori	8
H. pylori, Activity	3

- active inflammation : neutrophil
- dysplasia grade : low grade > high grade
- Helicobacter pylori : x20 > x400
- No missed case : malignancy, reactive atypia

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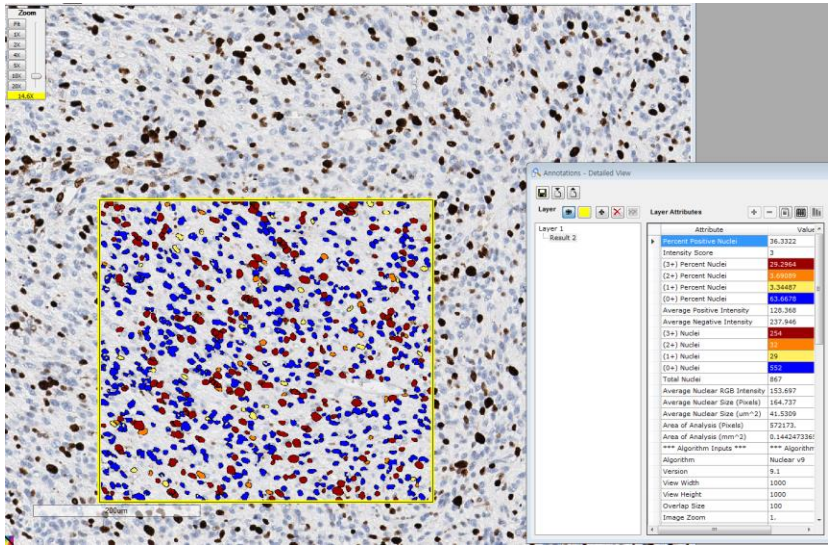
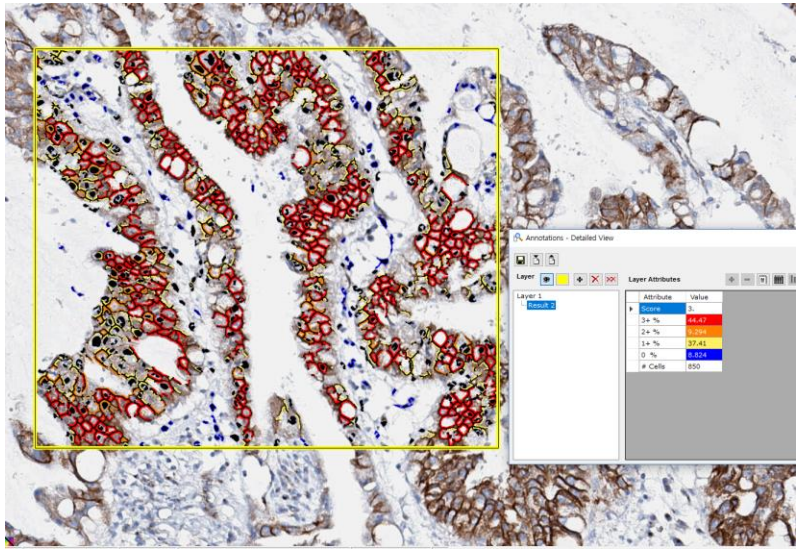
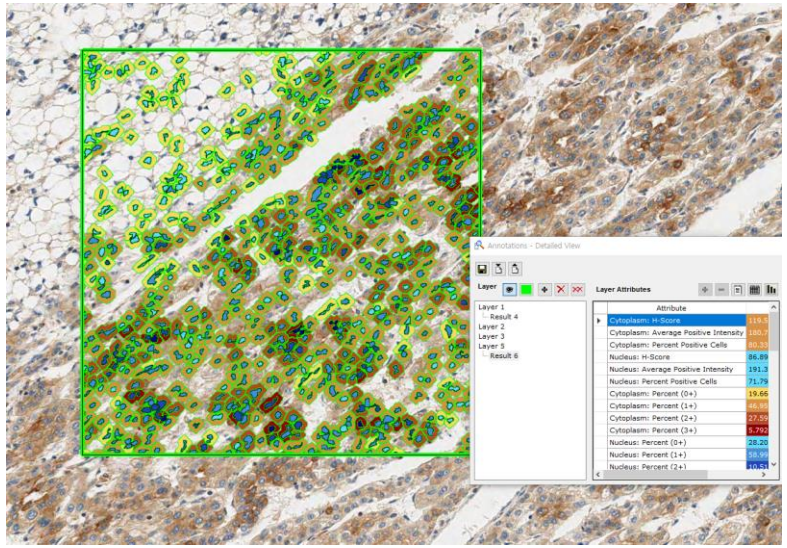
Quantification (I) : Biomarker



Nuclear staining, Ki-67



Membrane staining, Her-2



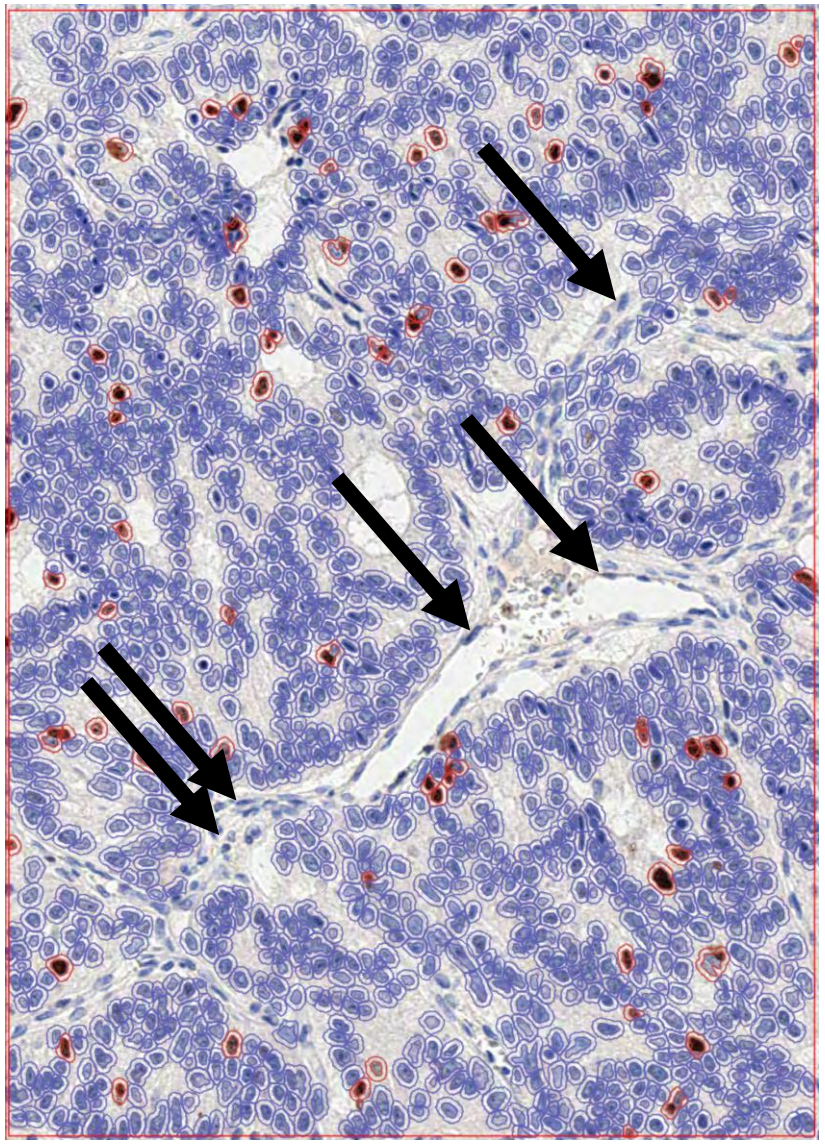
Cytoplasmic staining, Hep-par1

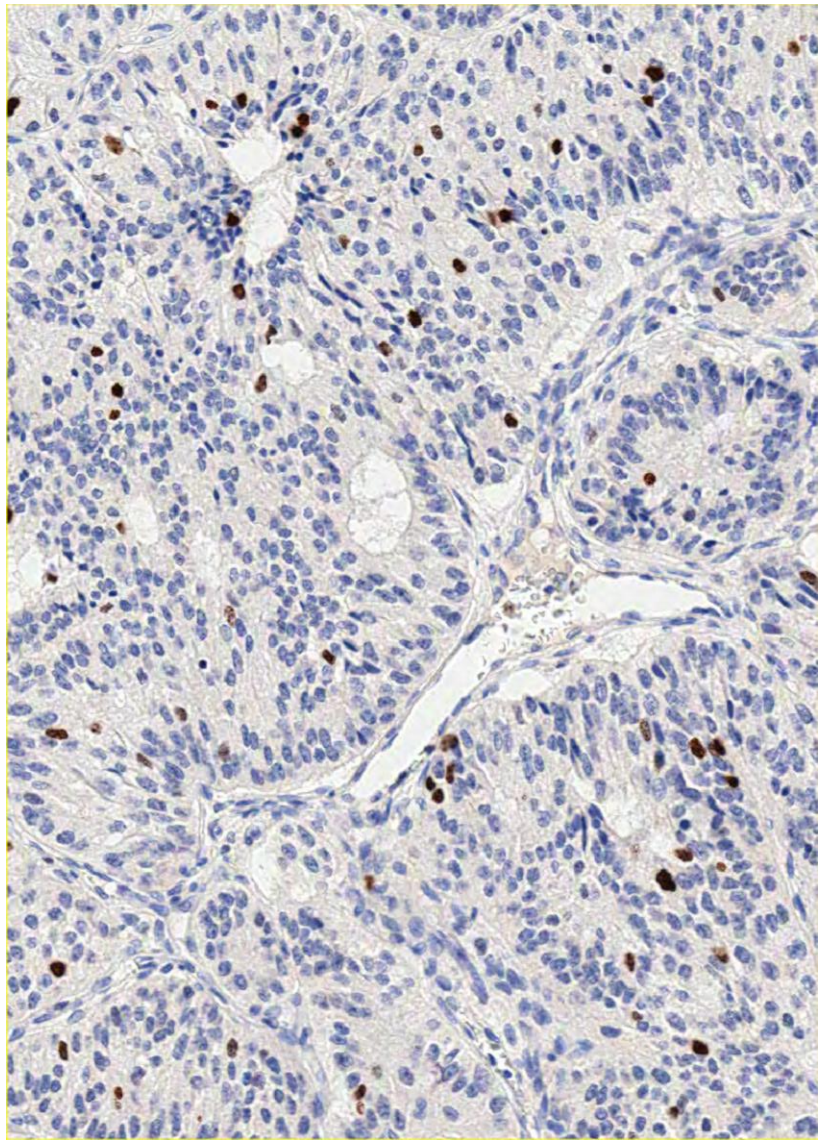
Usage : biomarker evaluation eg. Hormone receptor, HER2, proliferation index, PD-L1

Limitation:

- automatic tumor cell identification among various cells
- Artifact : tissue, staining

➔ Need manual correction





Segmentation by QuPath (free software)
Manual removal of nontumor cells or artifact
➔ 4.24% 75/1770, Neuroendocrine tumor, G2 : **tumor grading**

Quantification (II): multiplex IHC

Methods 70 (2014) 46–58

Contents lists available at ScienceDirect

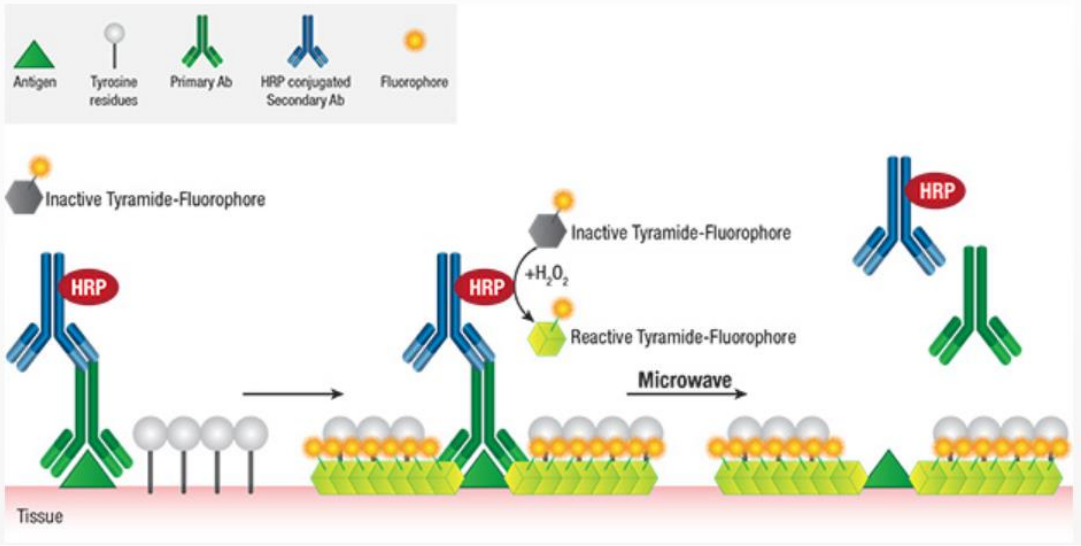
Methods

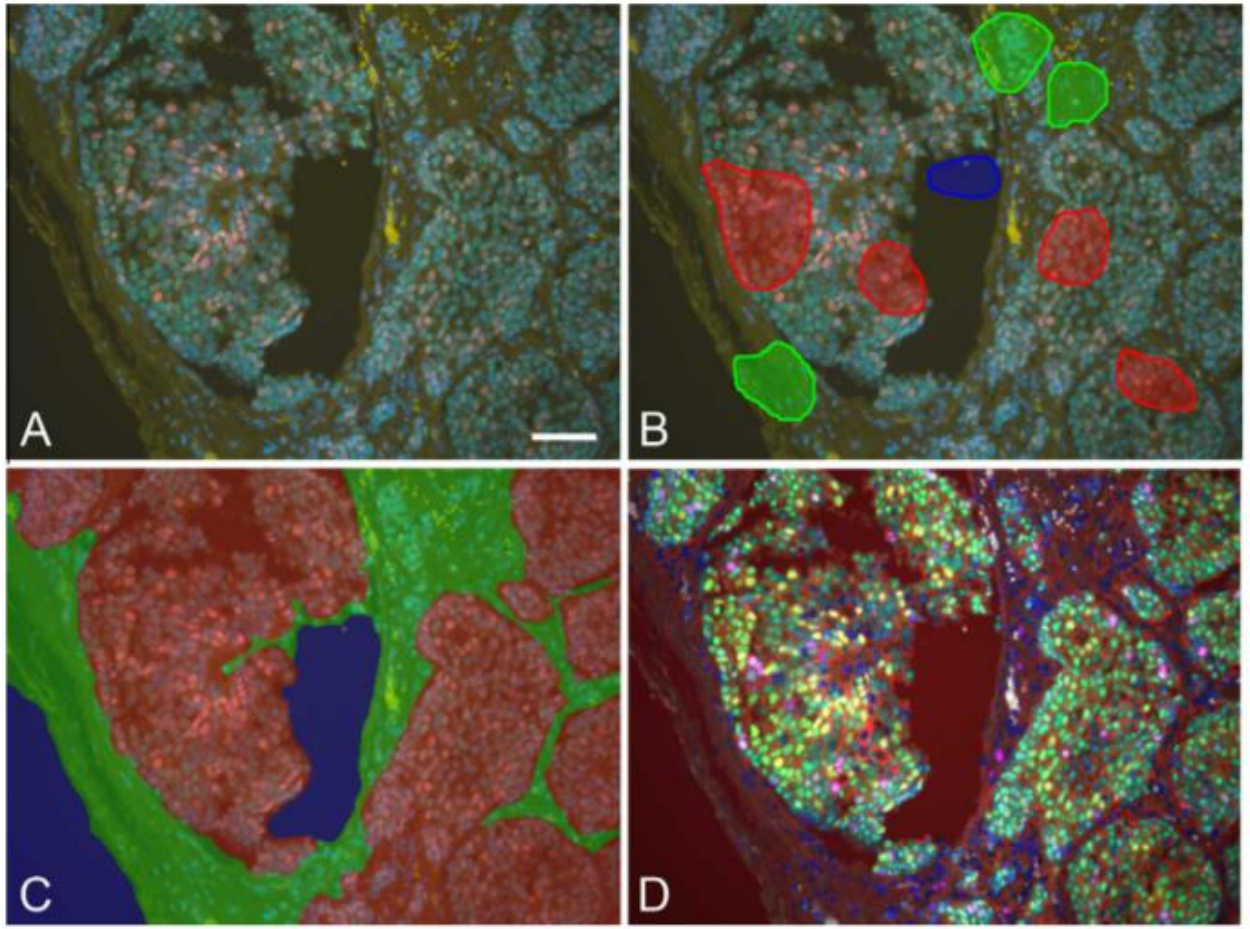
journal homepage: www.elsevier.com/locate/ymeth

Multiplexed immunohistochemistry, imaging, and quantitation: A review, with an assessment of Tyramide signal amplification, multispectral imaging and multiplex analysis

Edward C. Stack, Chichung Wang, Kristin A. Roman, Clifford C. Hoyt *

PerkinElmer, Inc., Waltham, MA 02451, USA

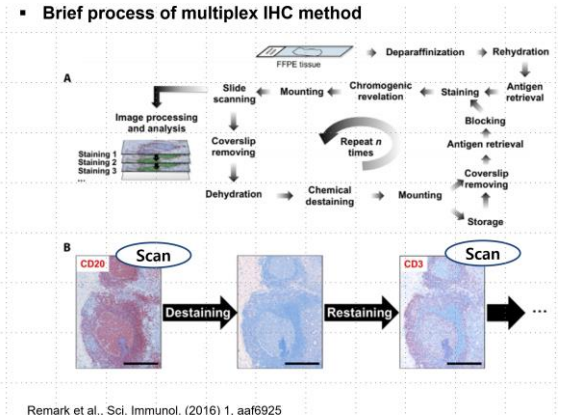


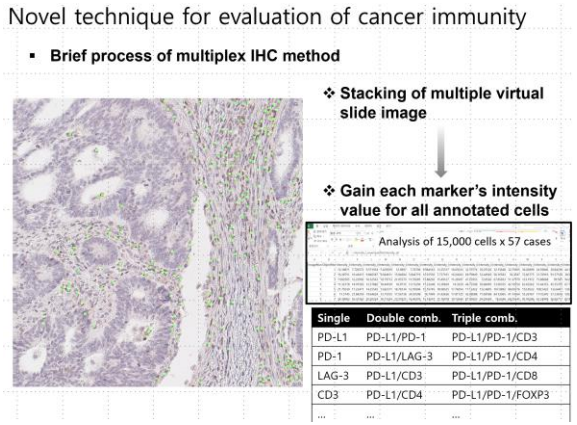


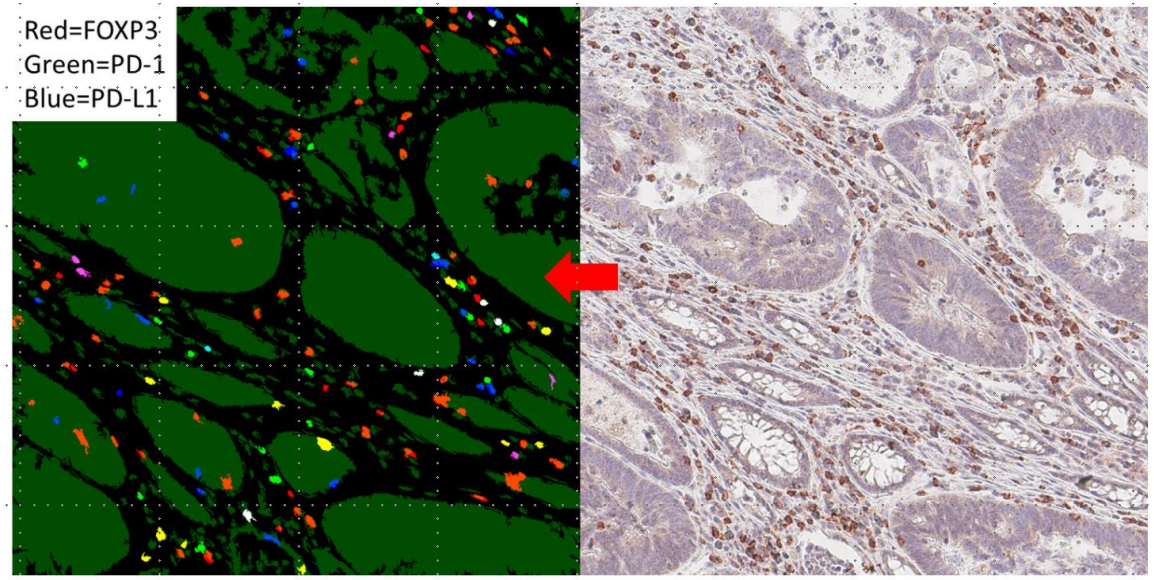
ER /PR / Her2 / Ki67

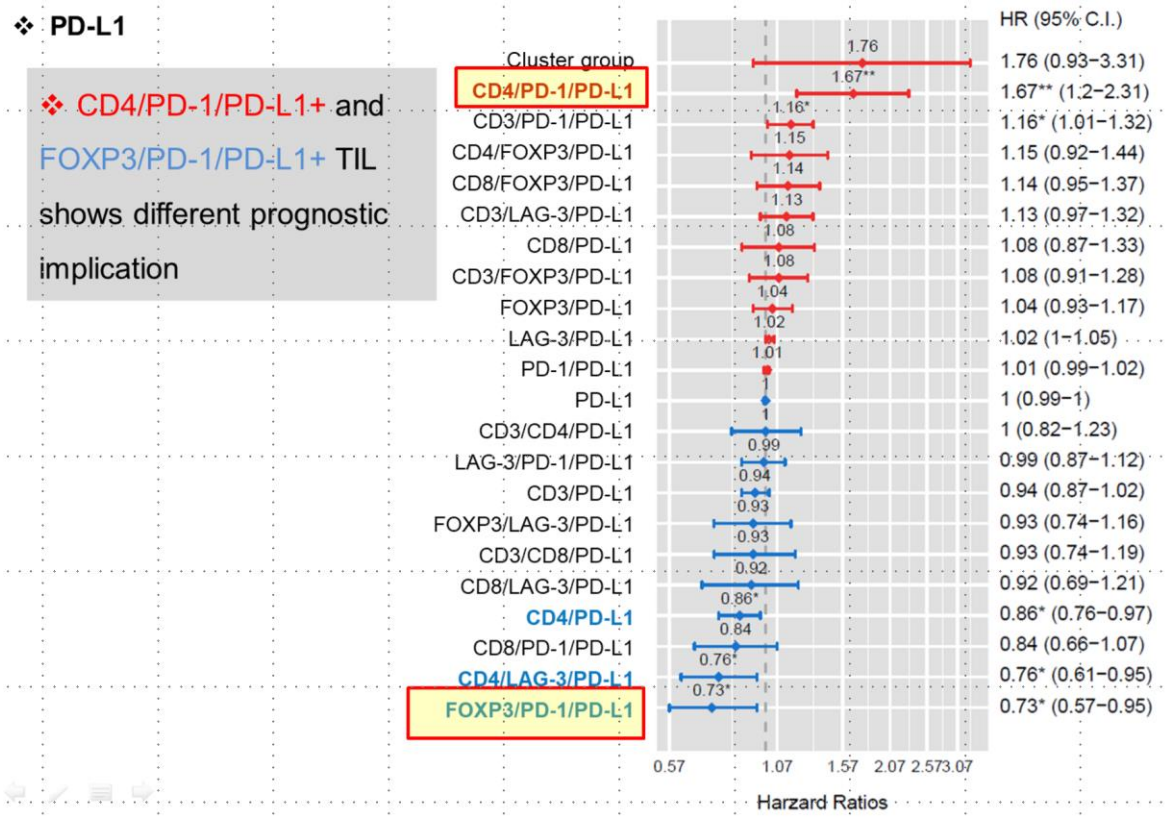
Quantification (II): multiplex IHC

multiplex IHC in CRC patients









Courtesy by YJ Kwak, Department of pathology, Seoul National university Hospital presented in the 7-th annual fall meeting of the Korean society of pathologists

Discrimination (I) : quantitative image feature

J Pathol Inform

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Research Article

Quantitative nucleic features are effective for discrimination of intraductal proliferative lesions of the breast

Masatoshi Yamada[1], Akira Saito[2], Yoichiro Yamamoto[3], Eric Cosatto[4], Atsushi Kurata[1], Toshitaka Nagao[5], Ayako Tateishi[6], Masahiko Kuroda[1]

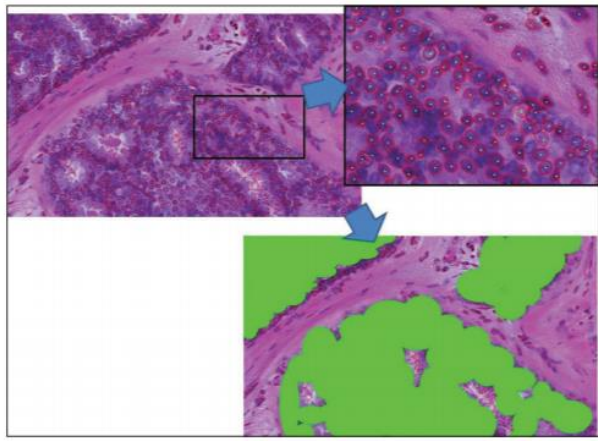


Figure 2: Example of nuclear contour extraction results. The enlarged partial position is on the upper right. Red lines indicate the automatically extracted nuclear contour line. Yellow dots indicate the nuclear center position. The lower image is a manually created masked image. Nuclear features were measured only on selected nuclei indicated in green areas

Table 2: Nuclear morphological parameters

Nucleus size and shape parameters			
Nucleus area size	Nucleus contour line length	Roundness	Long axis length
Short axis length	Ellipsoidal ratio	Contour line complexity	IDG1 area size
Nucleus density in tissue	Nuclear arrayment level		
Intranuclear texture parameters			
GLCM angular 2nd moment	GLCM contrast	GLCM homogeneity	GLCM entropy
IDG2 nucleus volume	IDG3-8	IDG9-14	IDG15-20
IDG7	IDG10	IDG11	IDG12
IDG13	IDG14	IDG15	IDG16
IDG21-26	Nuclear texture complex		

Average; variance; standard deviation; median, mode; 10%, 30%, 50% 70%, and 90% tile data; 80% based average variance, standard deviation, median, mode. GLCM: Gray level co-occurrence matrix, IDG: Integrated diffusion gradient, IDG1: Ratio of nucleus area size and rectangle box area (long × short axis), IDG2: Ratio of nucleus 3D volume to cuboid volume, IDG3-8: Total volume over 6 threshold intensity levels, IDG9-14: Increased volume over each threshold intensity level, IDG15-20: Counts for each threshold intensity level cluster, IDG 21-26: Image fractal dimensions for each threshold intensity level

Table 4b: Accuracy table

	Normal	UDH (%)	ADH (%)	LG-DCIS (%)	IM-DCIS (%)	HG-DCIS (%)
Normal		97.3	84.8	93.0	97.9	97.6
UDH			87.2	90.1	97.8	99.3
ADH				88.1	94.7	96.7
LG-DCIS					81.8	97.0
IM-DCIS						96.0
HG-DCIS						

UDH: Usual ductal hyperplasia, ADH: Atypical ductal hyperplasia, LG-DCIS: Low-grade ductal carcinoma *in situ*, IM-DCIS: Intermediate-grade ductal carcinoma *in situ*, HG-DCIS: High-grade ductal carcinoma *in situ*

Discrimination (I) : quantitative image feature

- Discrimination by digitalized image feature >

  Predicting non-small cell lung cancer prognosis by fully automated microscopic pathology image feature. Nat commun. 2016;7:12474

- Extract quantitative image feature : 790 items

AreaShape_Zernike_8_6.0.5.1
AreaShape_Zernike_8_6.0.6.1
Texture_DifferenceEntropy_MaskedHWithoutOverlap_3_90.0.7.1
Texture_DifferenceEntropy_MaskedHWithoutOverlap_3_45.0.8.1
Texture_DifferenceEntropy_MaskedHWithoutOverlap_3_90.0.8.1
Texture_Contrast_MaskedHWithoutOverlap_3_90.0.9.1
Texture_InfoMeas2_MaskedHWithoutOverlap_3_90.0.1.2
Texture_SumVariance_MaskedHWithoutOverlap_3_45.0.3.2
AreaShape_Zernike_6_0.0.4.2

- ***Quantitative image features cannot be understood or perceived by pathologist***

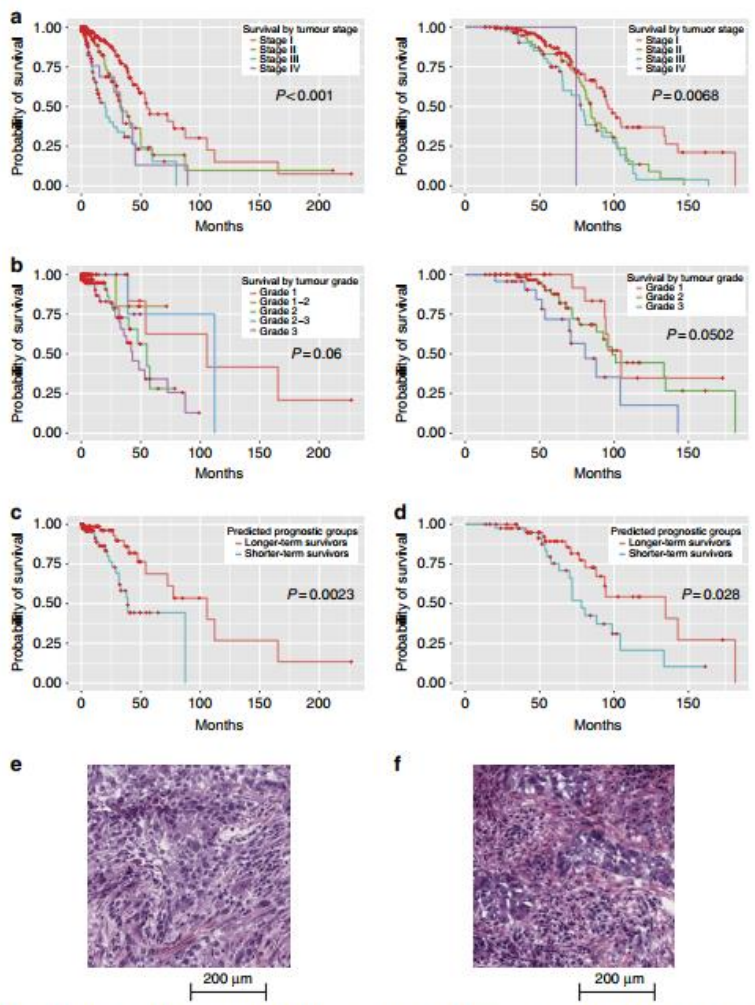
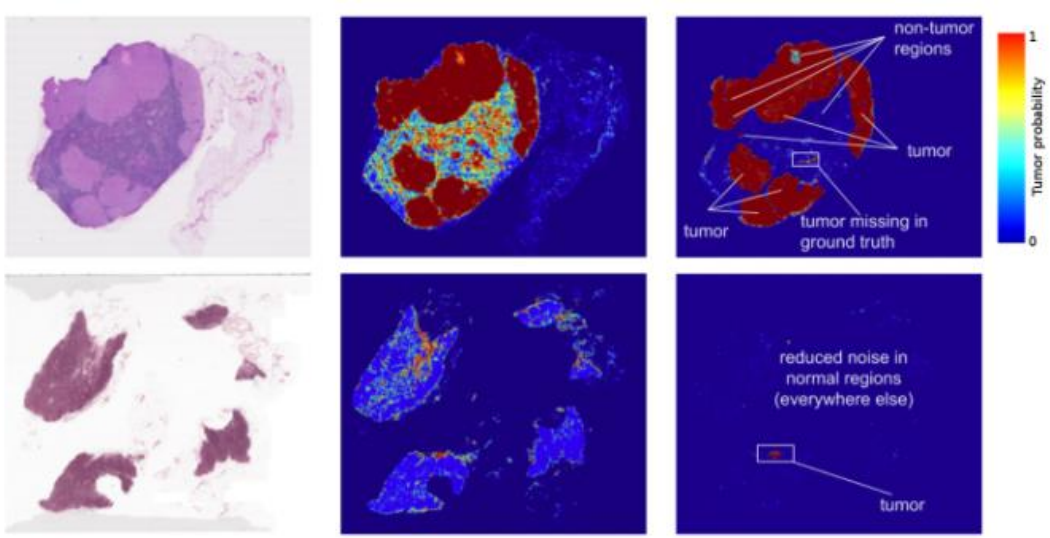


Figure 3 | Quantitative image features predicted the survival outcomes of stage I lung adenocarcinoma patients. (a) Kaplan–Meier curves of lung

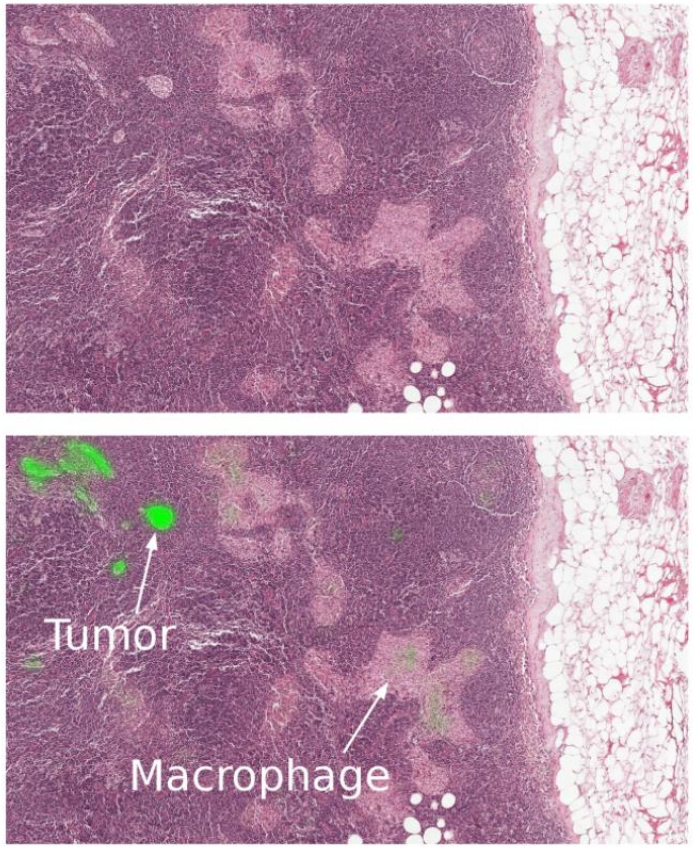
Discrimination (II) : Deep learning

Detecting Cancer Metastases on Gigapixel Pathology Images

Yun Liu[1*], Krishna Gadepalli[1], Mohammad Norouzi[1], George E. Dahl[1],
Timo Kohlberger[1], Aleksey E
Aleksei Timofeev[2], Philip Q. Nels
Lily Peng[1], an
{liuyun,mnorouzi,gdahl
[1]Google Brain, [2]Goog
Mountain



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.



A closeup of a lymph node biopsy. The tissue contains a breast cancer metastasis as well as macrophages, which look similar to tumor but are benign normal tissue. Our algorithm successfully identifies the tumor region (bright green) and is not confused by the macrophages.

- More sensitive than pathologist, but some false positive result
- Lack of other disease pattern
- ***Assisting pathologist, not primary role***

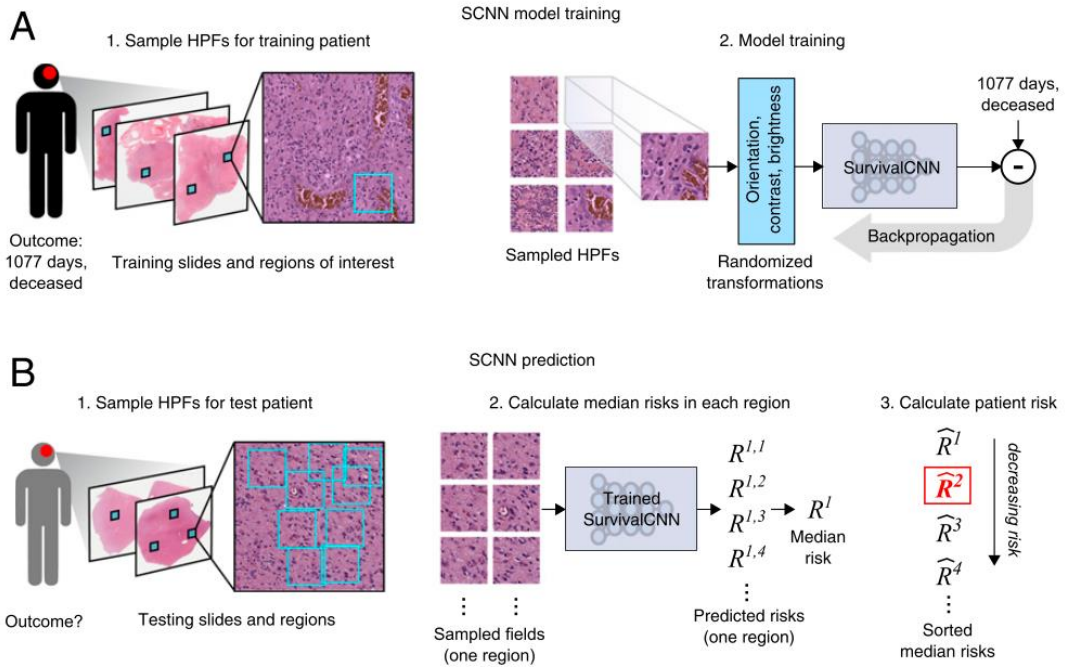
Find new prognostic groups

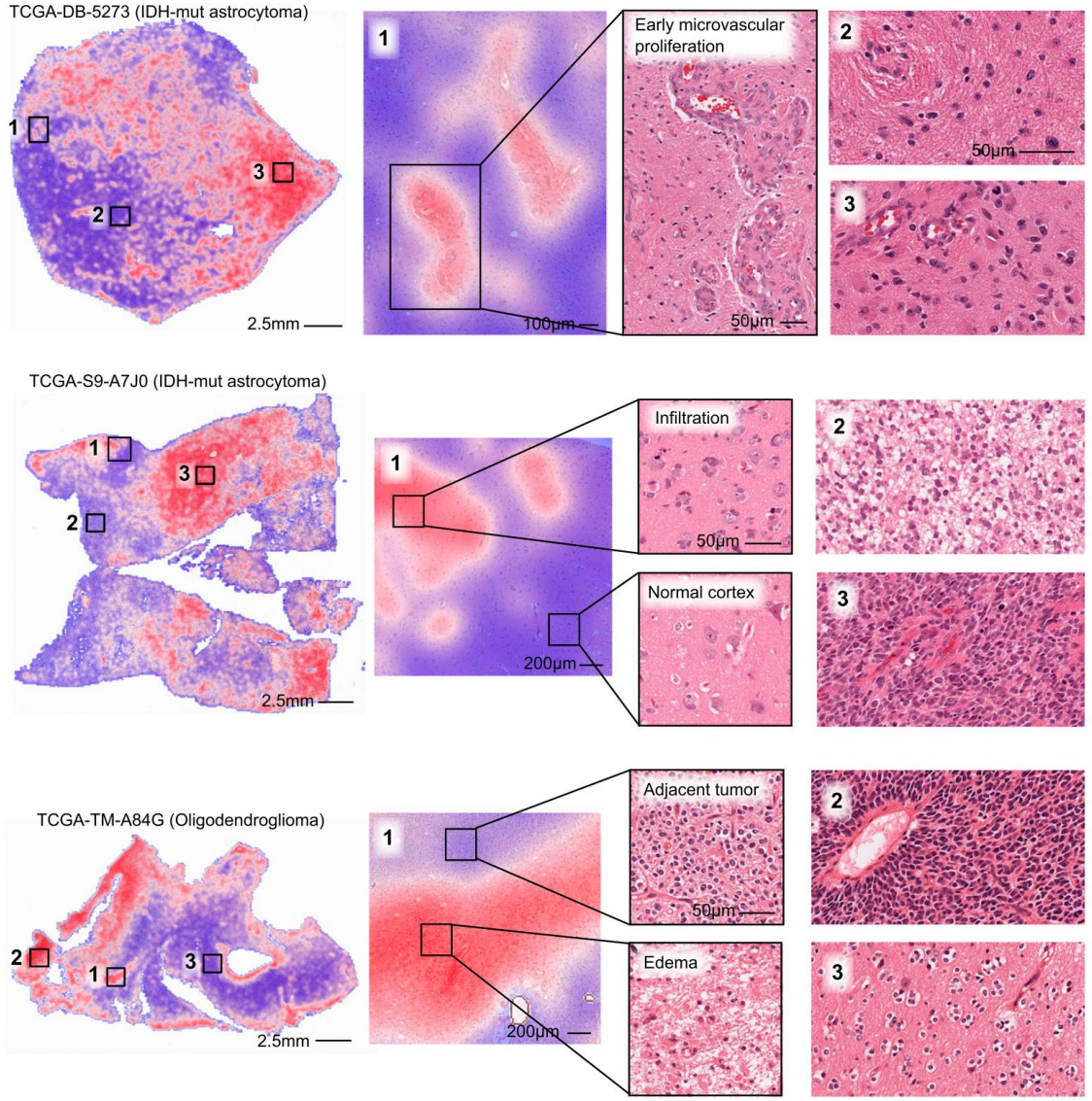
Predicting cancer outcomes from histology and genomics using convolutional networks

Pooya Mobadersany[a], Safoora Yousefi[a], Mohamed Amgad[a], David A. Gutman[b], Jill S. Barnholtz-Sloan[c], José E. Velázquez Vega[d], Daniel J. Brat[e], and Lee A. D. Cooper[a,f,g,1]

[a]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA 30322; [b]Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322; [c]Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH 44106; [d]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322; [e]Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611; [f]Winship Cancer Institute, Emory University, Atlanta, GA 30322; and [g]Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA 30322

Edited by Bert Vogelstein, Johns Hopkins University, Baltimore, MD, and approved February 13, 2018 (received for review October 4, 2017)





Outline

- **Introduction of digital pathology**
- **Digital pathology for primary diagnosis**
  - Component of digital pathology system for primary diagnosis
  - Digital pathology workflow, SNUH
  - Issues in implementation of digital pathology system
- **Digital pathology for research**
  - Computational pathology : quantification, discrimination, prediction
  - Reconstruction
- **New technique for digital pathology**
  - Slide-free non-destructive pathology

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Slide-free non-destructive pathology

nature biomedical engineering

ARTICLES

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Light-sheet microscopy for slide-free non-destructive pathology of large clinical specimens

Adam K. Glaser[1†], Nicholas P. Reder[2†], Ye Chen[1], Erin F. McCarty[2], Chengbo Yin[1], Linpeng Wei[1], Yu Wang[1], Lawrence D. True[2] and Jonathan T. C. Liu[1*]

For the 1.7 million patients per year in the US who receive a new cancer diagnosis, treatment decisions are largely based on

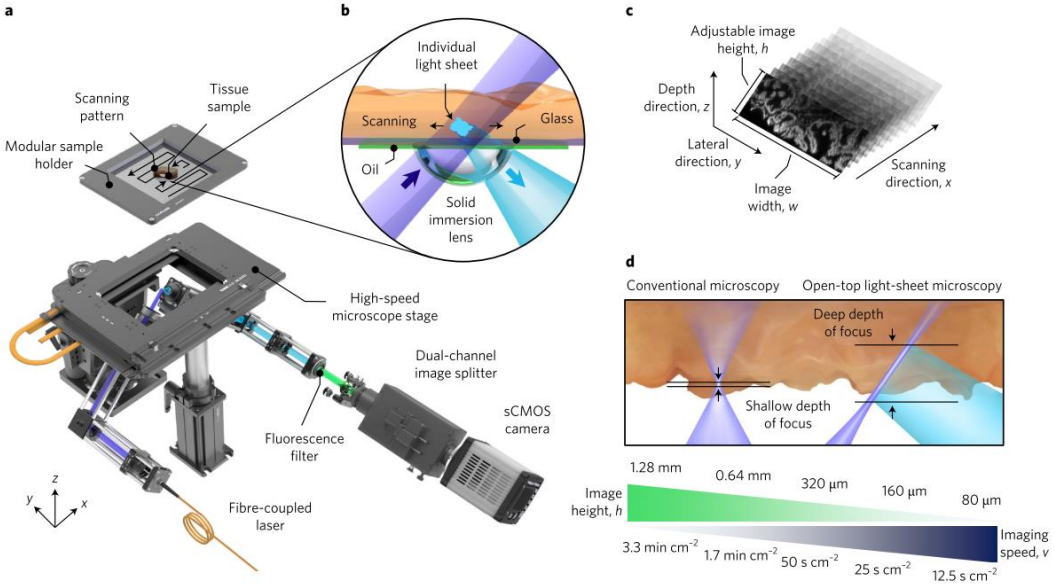
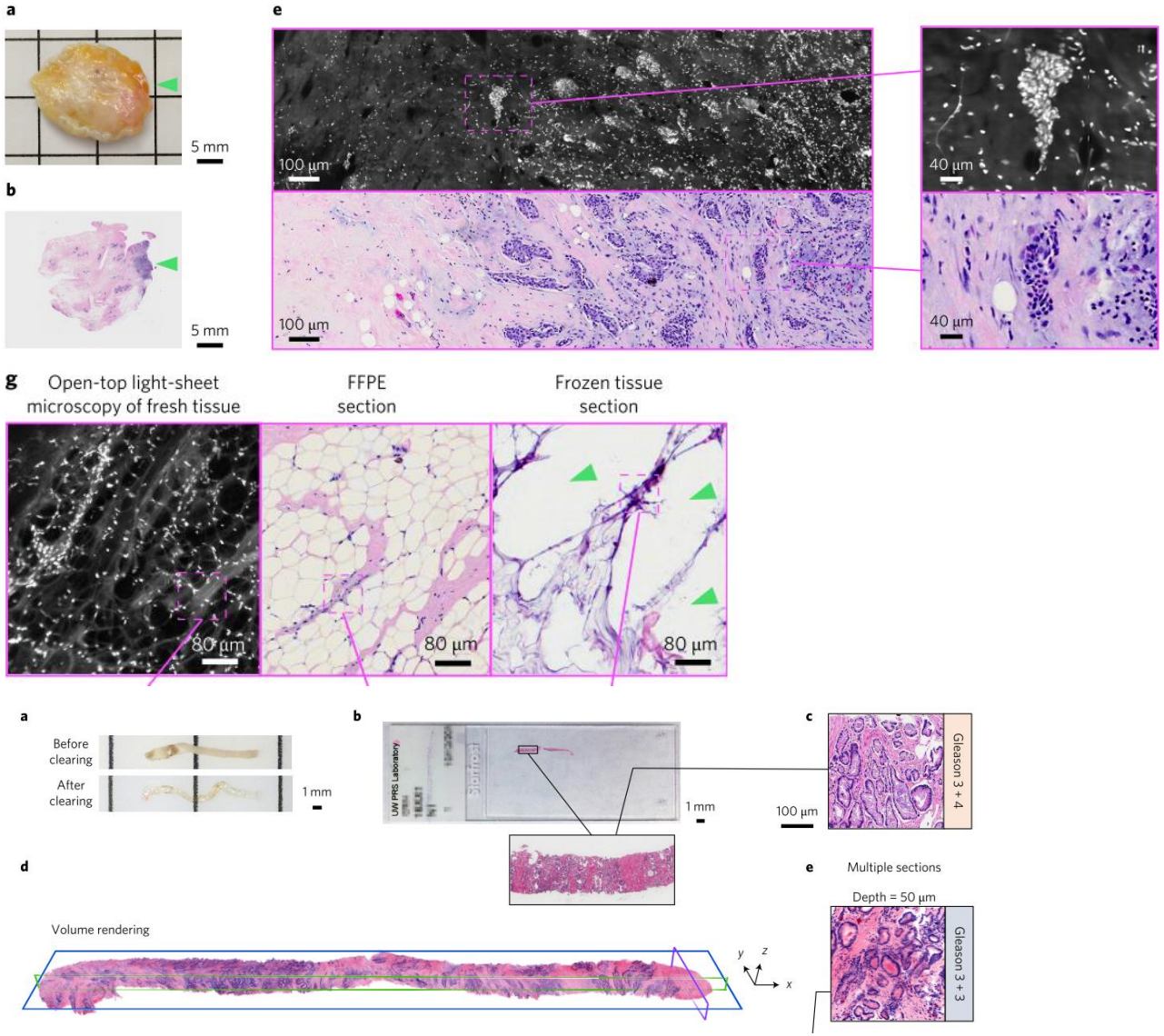
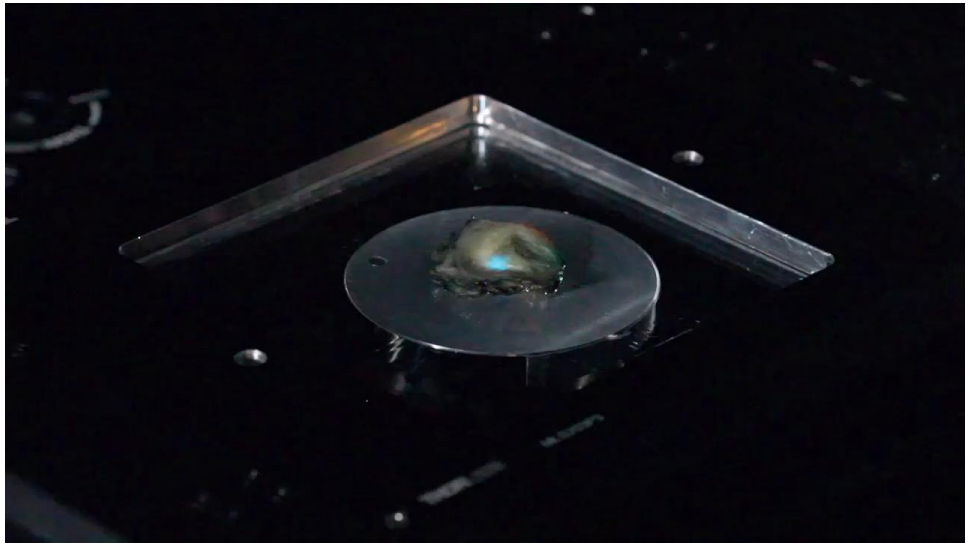
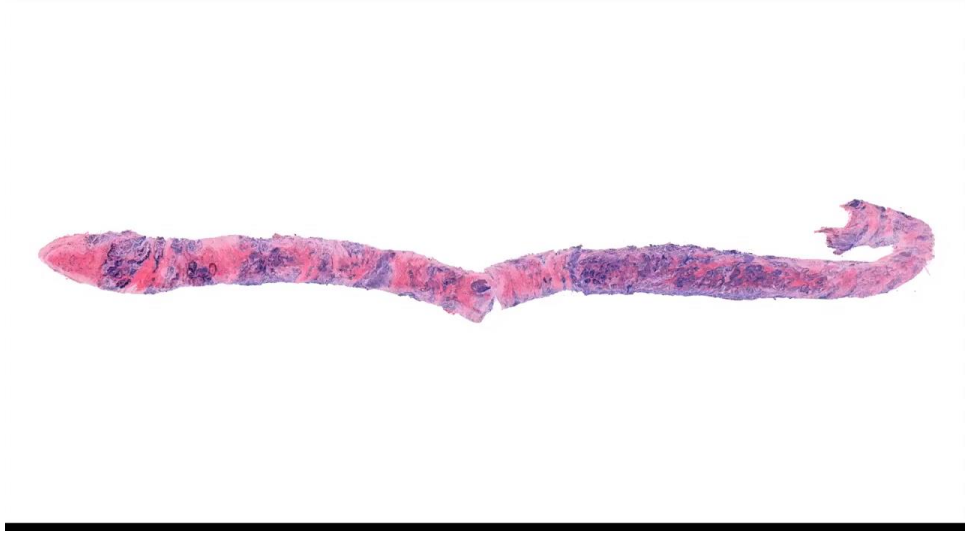


Figure 1 | Open-top light-sheet microscope for clinical pathology. a, An illumination light sheet enters the bottom surface of a tissue sample at an oblique 45° angle (purple). The specimen is placed on a modular glass-plate sample holder, which is inserted into a two-axis translation stage and scanned in a







Closing

- Virtual slide : replaceable system of light microscopy: practical problems remained
- Numerous research algorisms vs few clinical use: standization of images
- Future of digital pathology

To save pathologist's time

: find tumor, mitosis, micro-organism

➔ quantification, measurement, reporting

To help pathologist's decision

: segmentation and classification of cell and tissue

➔ support diagnosis, grading, pattern recognition

To find new histologic feature or subtype

: survival, genetic information

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