Highlighting Challenges for Machine Learning in the Pathology Clinic through Specific Use Cases

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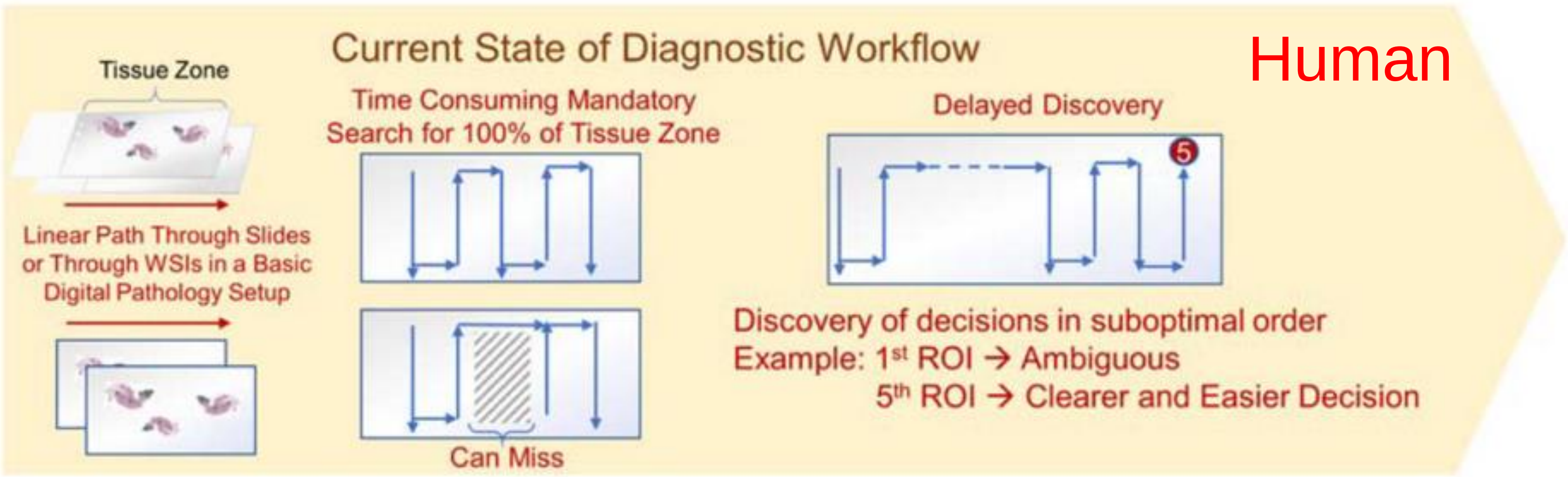
https://cancer.osu.edu/news-and-media/news/digital-pathology-could-improve-accuracy-timeliness-of-cancer-diagnosis

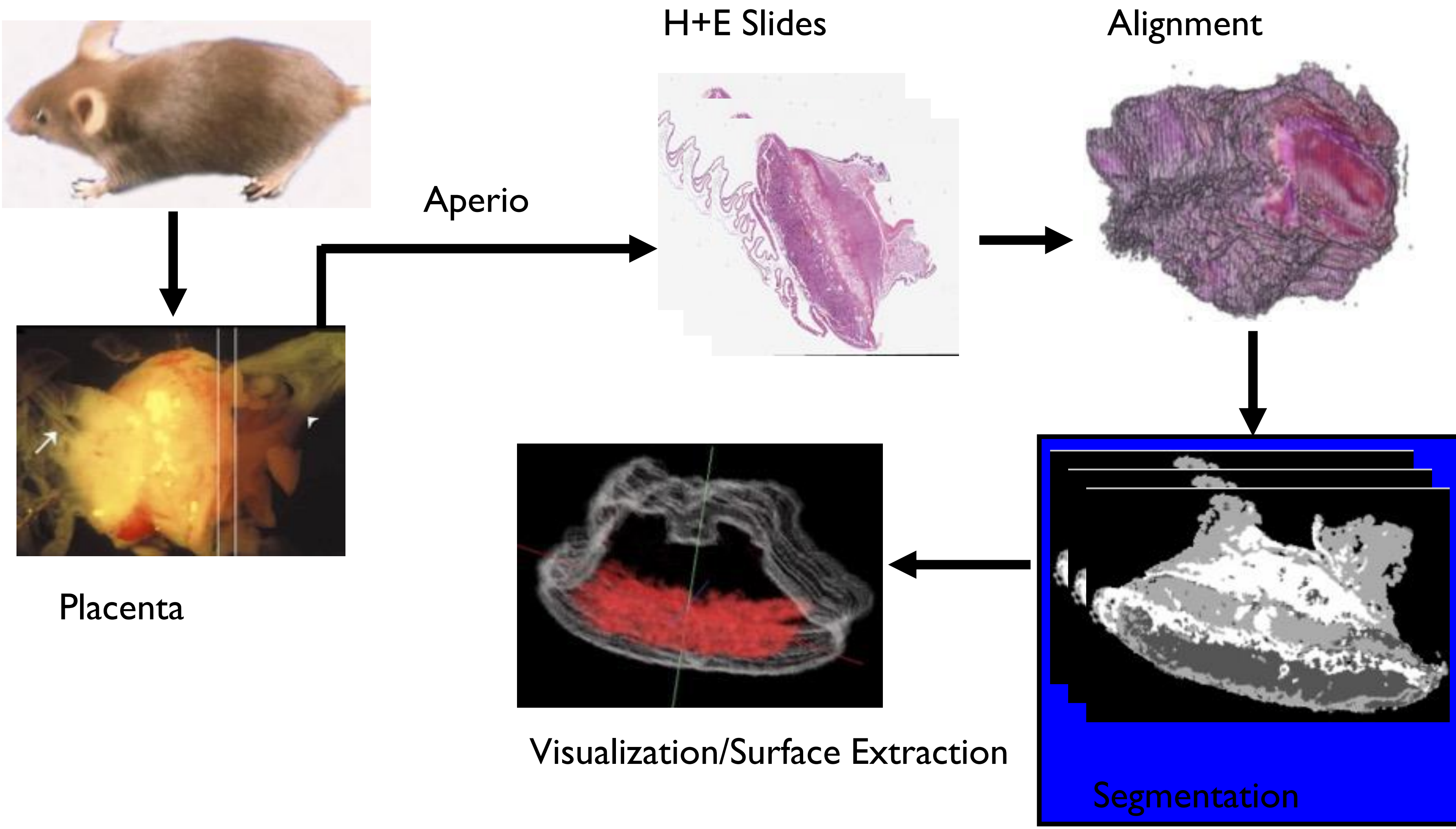
Typical clinical workflows



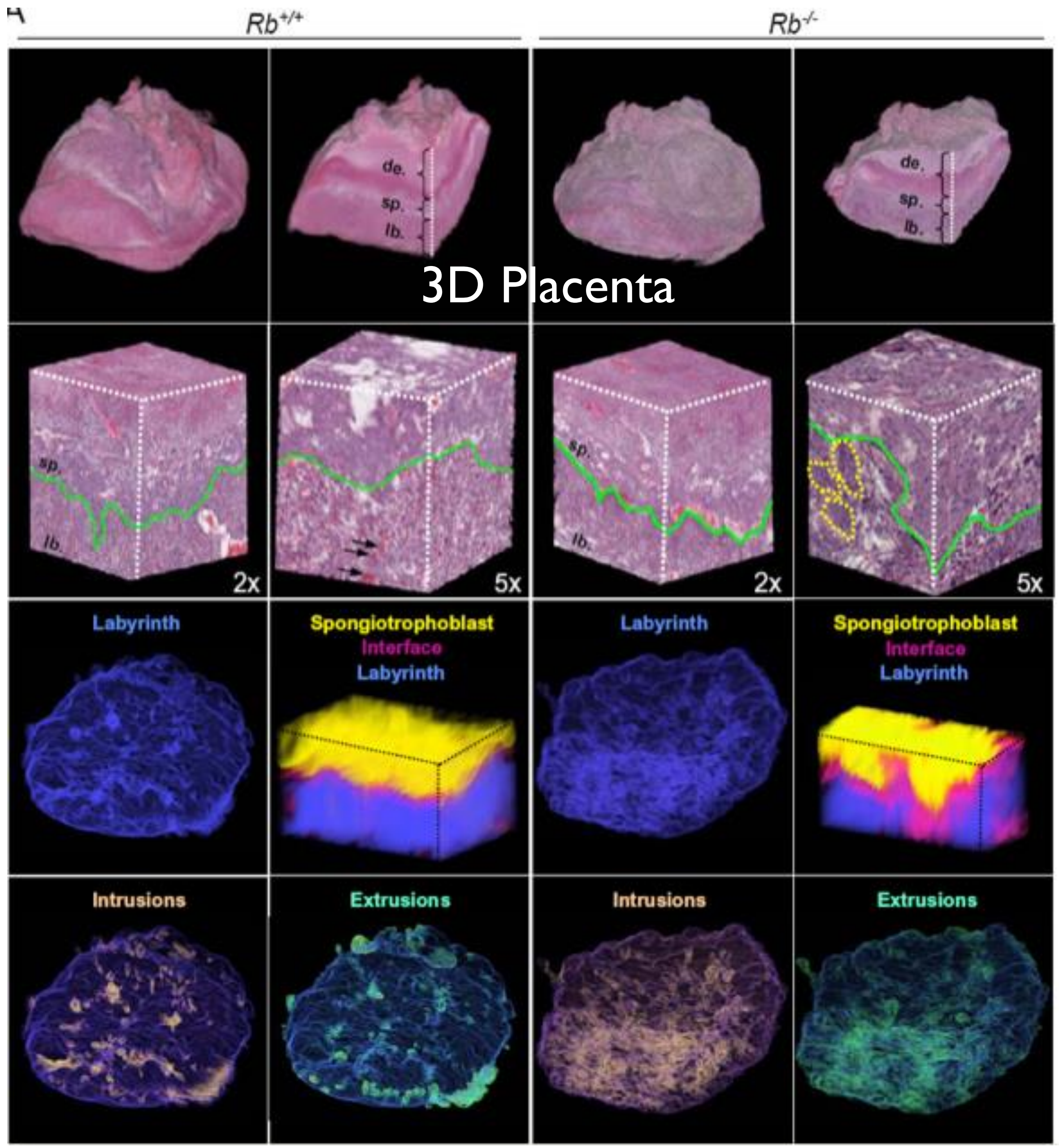
Domain-specific Search Task

doi: 10.1097/PAP.0000000000000264

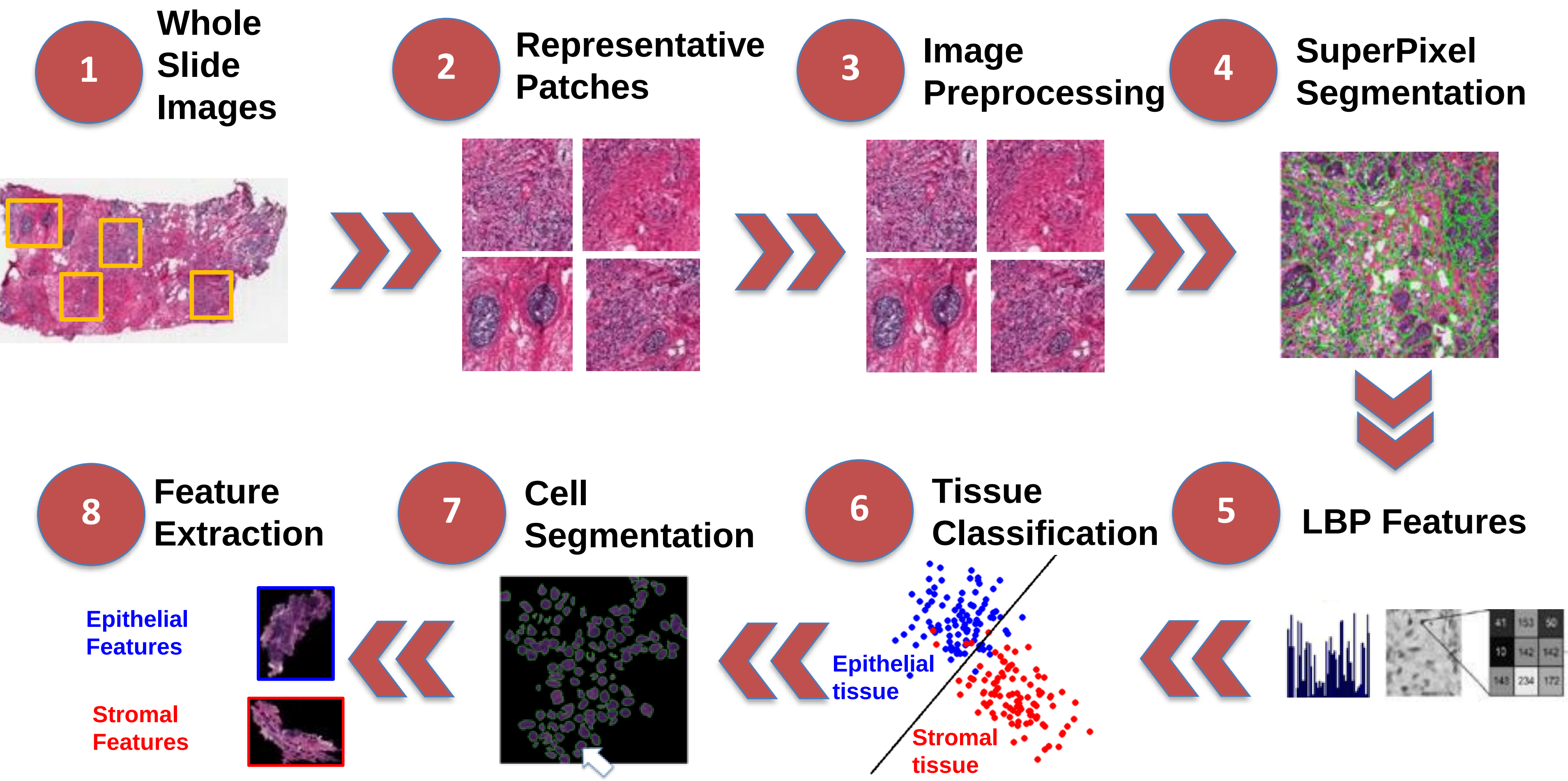
H&E Processing - circa 2000s



H&E Reveal A Lot About Phenotypes



OSU/Stanford/GaTech - Circa 2010s



JIM Review

doi: 10.1111/joim.13030

Artificial intelligence as the next step towards precision pathology

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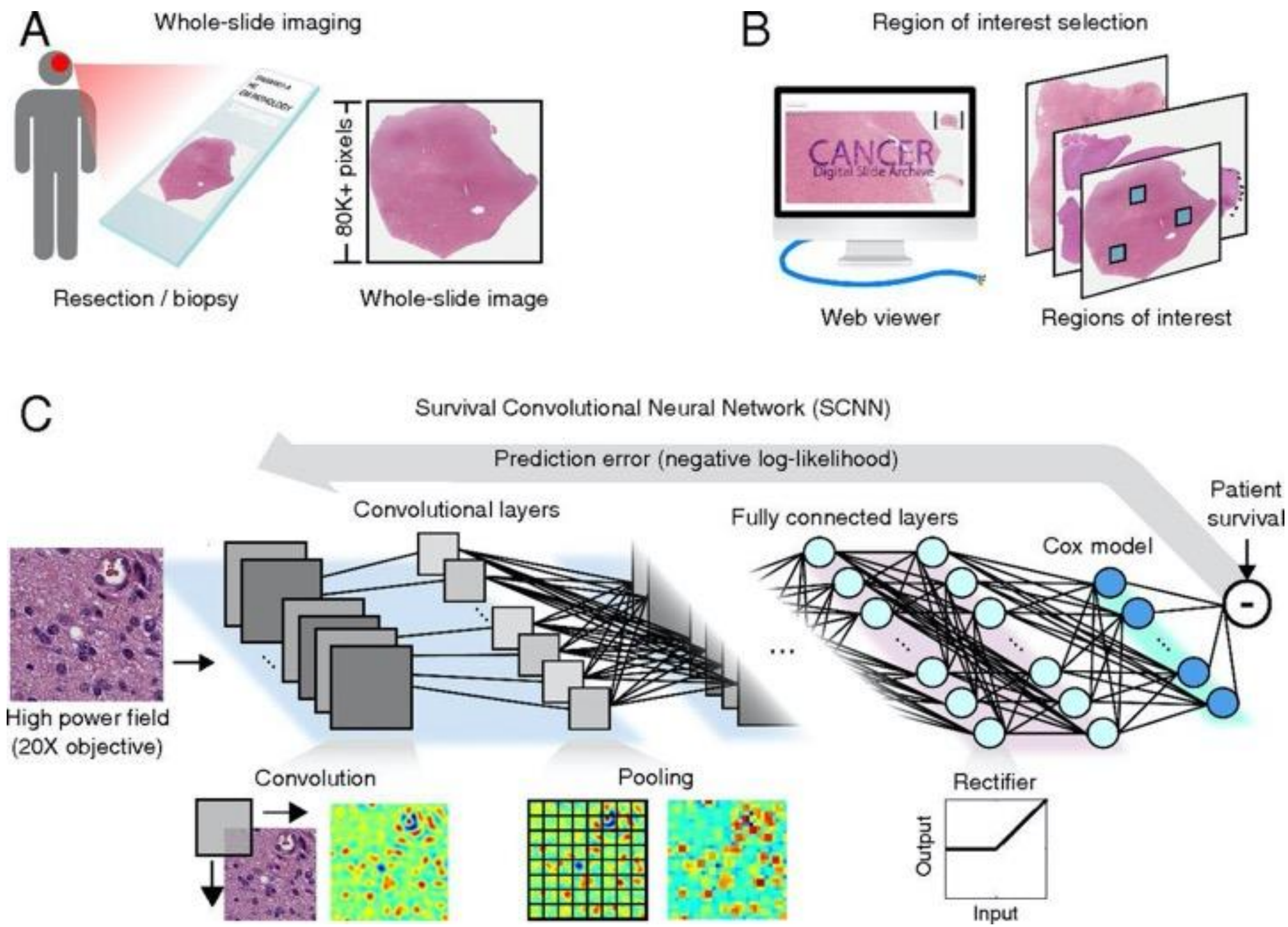
From the [1]Department of Oncology and Pathology; and [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Abstract. Acs B, Rantalainen M, Hartman J (Karolinska Institutet, Stockholm, Sweden) Artificial intelligence as the next step towards precision pathology. *J Intern Med*; 2020; **288**: 62–81.

Pathology is the cornerstone of cancer care. The need for accuracy in histopathologic diagnosis of cancer is increasing as personalized cancer therapy requires accurate biomarker assessment. The appearance of digital image analysis holds promise to improve both the volume and precision of histomorphological evaluation. Recently, machine learning, and particularly deep learning, has enabled rapid advances in computational pathology. The integration of machine learning into routine care will be a milestone for the healthcare sector in the next decade, and histopathology is right at the centre of this revolution. Examples of potential high-value machine learning applications include both model-based assessment of routine diagnostic features in pathology, and the ability to extract and identify novel features that provide insights into a disease. Recent groundbreaking results have demonstrated that applications of machine learning methods in pathology significantly improves metastases detection in lymph nodes, Ki67 scoring in breast cancer, Gleason grading in prostate cancer and tumour-infiltrating lymphocyte (TIL) scoring in melanoma. Furthermore, deep learning models have also been demonstrated to be able to predict status of some molecular markers in lung, prostate, gastric and colorectal cancer based on standard HE slides. Moreover, prognostic (survival outcomes) deep neural network models based on digitized HE slides have been demonstrated in several diseases, including lung cancer, melanoma and glioma. In this review, we aim to present and summarize the latest developments in digital image analysis and in the application of artificial intelligence in diagnostic pathology.

Keywords: artificial intelligence, deep learning, digital image analysis, digital pathology, machine learning, pathology.



Pooya Mobadersany et al. PNAS 2018;115:13:E2970-E2979

Deep Learning In Cancer Pathology

Breast

DL algorithms reach comparable or better performance than human pathologists:

- Breast cancer micrometastasis (lymph nodes)
- Detect tubule formation (corresponding to Oncotype DX and tumor grade in ER+ breast cancer)

Discrimination of benign vs malignant based on stromal compartment

Discrimination of normal tissue, atypia, DCIS, and invasive carcinoma

Prostate

DL algorithms reach comparable or better performance than human pathologists:

- Gleason grading (better risk stratification)

Slide level cancer detection

SPOP mutation status

Lung

Classify normal, adenocarcinoma, squamous cell carcinoma

- Prediction of recurrence in early-stage non-small cell lung cancer (using nuclear orientation, nuclear shape, and tumor architecture)
- Predict mutation status of six genes in lung adenocarcinoma - KRAS, FAT1, TP53, SETBP1, EGFR, STK11

Brain

- Prognosis in gliomas (incorporated genomic data too)

Skin

- Prognosis in early stage melanoma - lymphocyte content most important factor to predict outcome

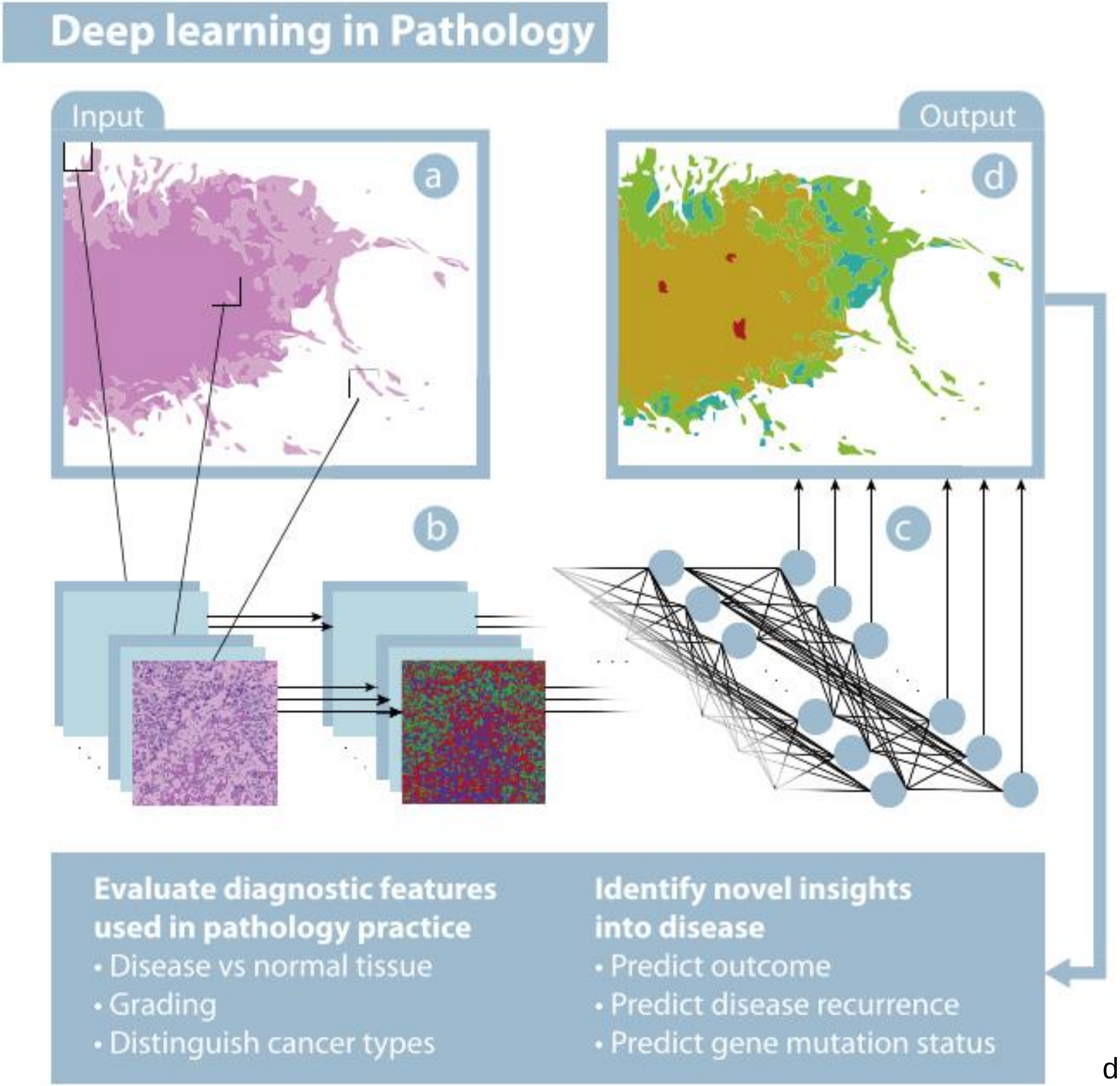
GI

- Predict microsatellite instability from gastric and colorectal cancer

Pancancer

- Local patterns and overall structural patterns of TILs are differentially represented among tumor types and tumor molecular subtypes (the patterns are differentially related to survival amongst different tumor types)

doi:10.1111/joim.13030



doi:10.1111/joim.13030

Attaining the Gold Standard of Diagnosis

- Also called Criterion Standard!
- Diagnostic test or criteria best available under reasonable conditions
- Ideally has sensitivity and specificity of 100% with respect to disease

[Is histopathology still the gold standard?]

[Article in Dutch]

M A den Bakker [1]

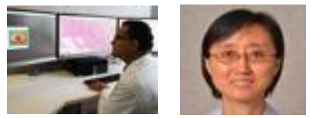
Affiliations + expand

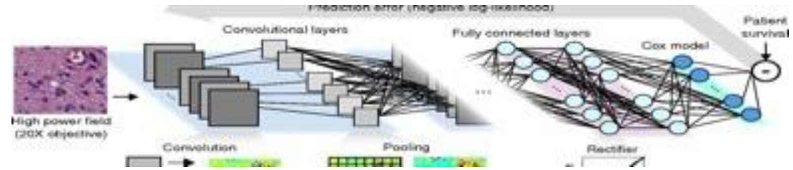
PMID: 28120732

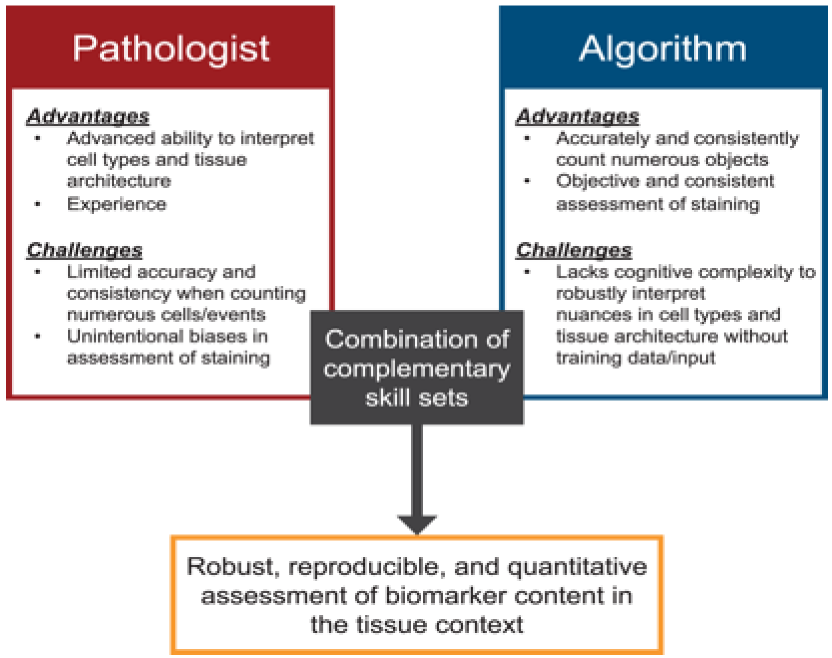
Abstract

In the diagnostic process, microscopical analysis is considered to be the gold standard in determining the presence and nature of a disease. In some cases, in particular in rare diseases and in precursor lesions in which pathological changes have not yet fully developed, histological assessment is subject to diagnostic uncertainty. This uncertainty may be further compounded by the increasing tendency to submit small biopsies which may only harbour part of a pathological process. Several strategies may be adopted to increase the precision of histological analysis. While it is reasonable to assume that these strategies will lead to improved performance, systematic research to confirm this assumption is lacking. It is important to be aware of the limitations of histopathological testing.

Us & Machines To Attain The Gold Standard



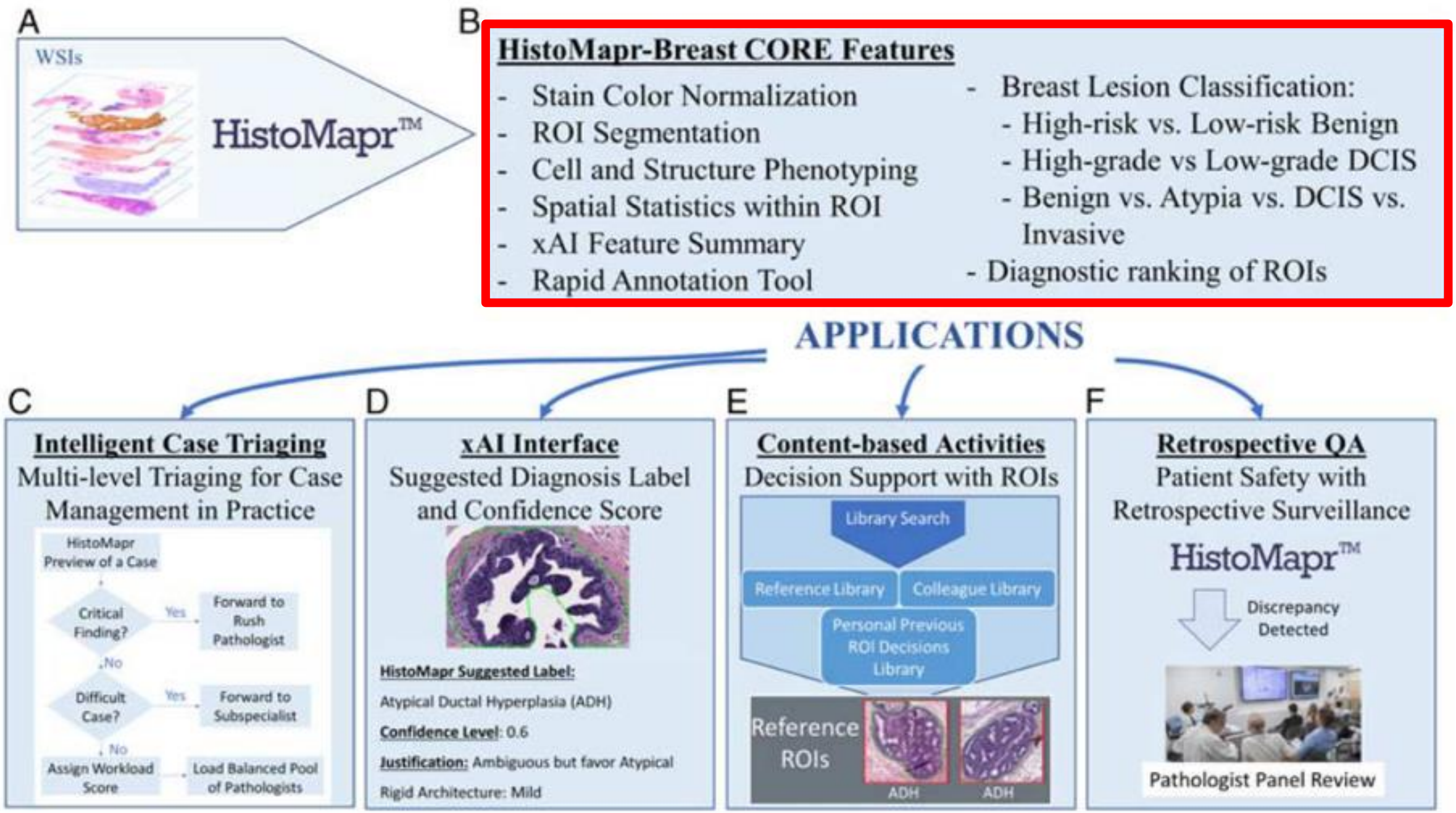




From: The Gold Standard Paradox in Digital Image Analysis: Manual Versus Automated Scoring as Ground Truth

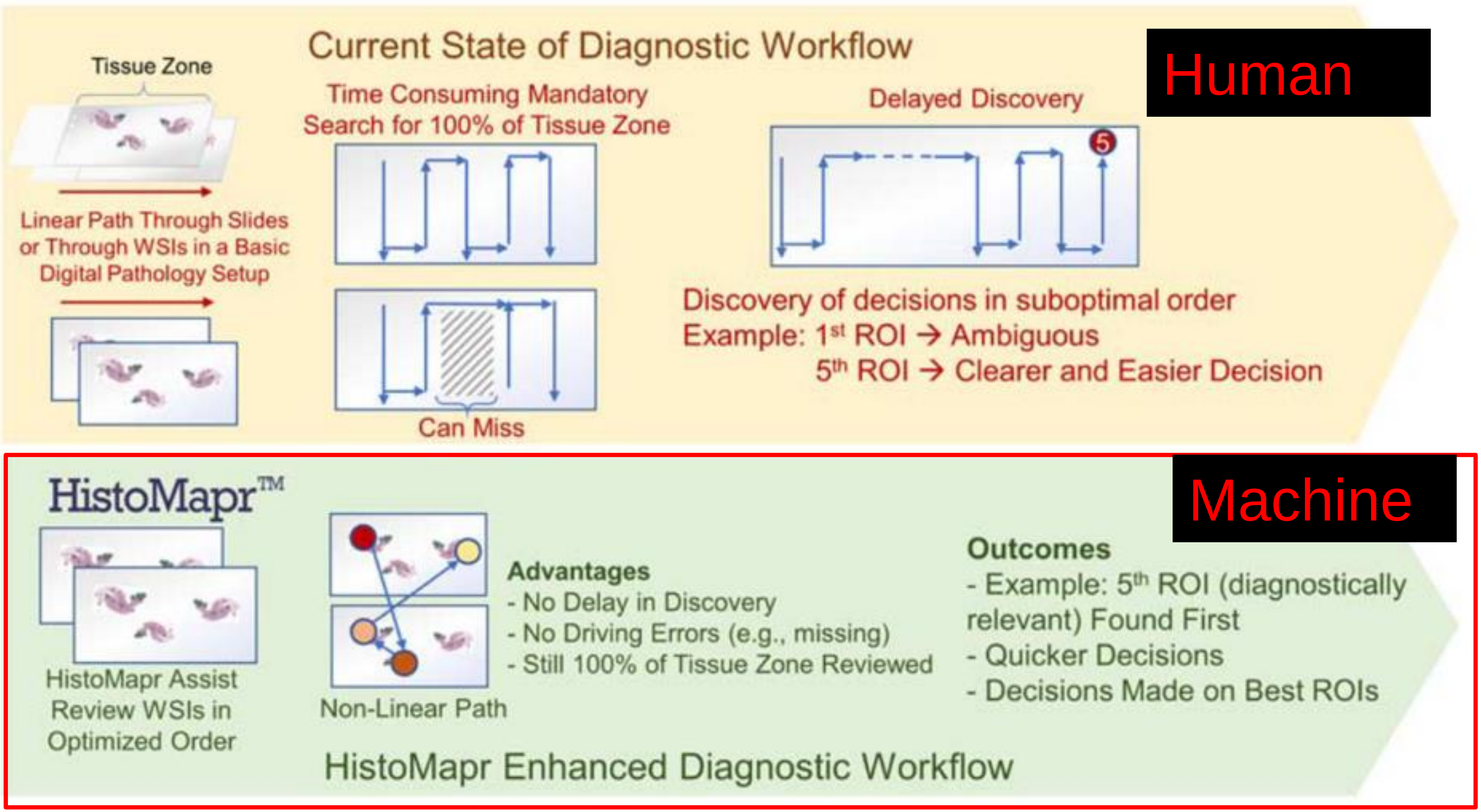
Arch Pathol Lab Med. 2017;141(9):1267-1275. doi:10.5858/arpa.2016-0386-RA

Machines @ Work for the Gold Standard



doi: 10.1097/PAP.0000000000000264

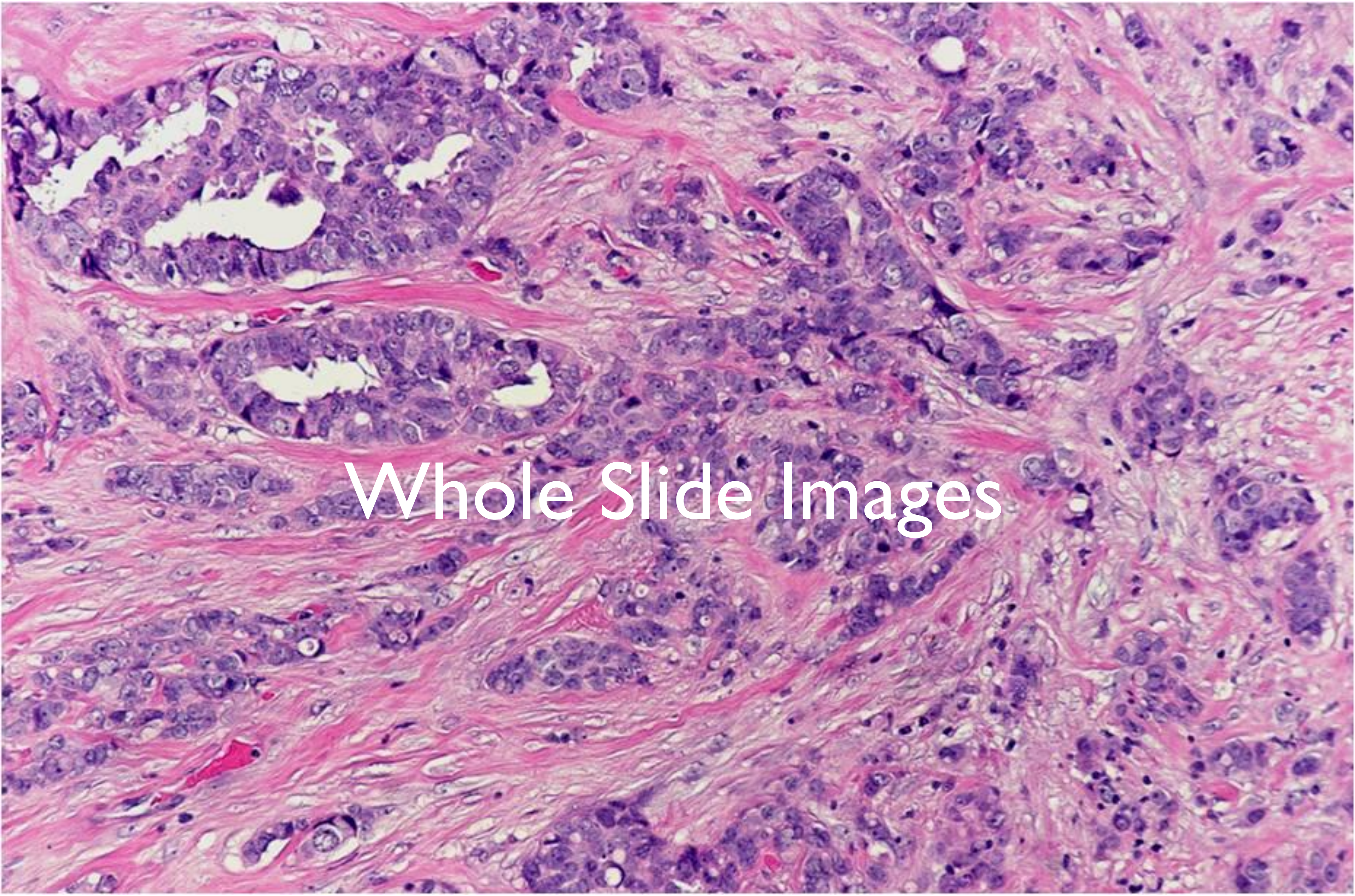
Machines @ Work



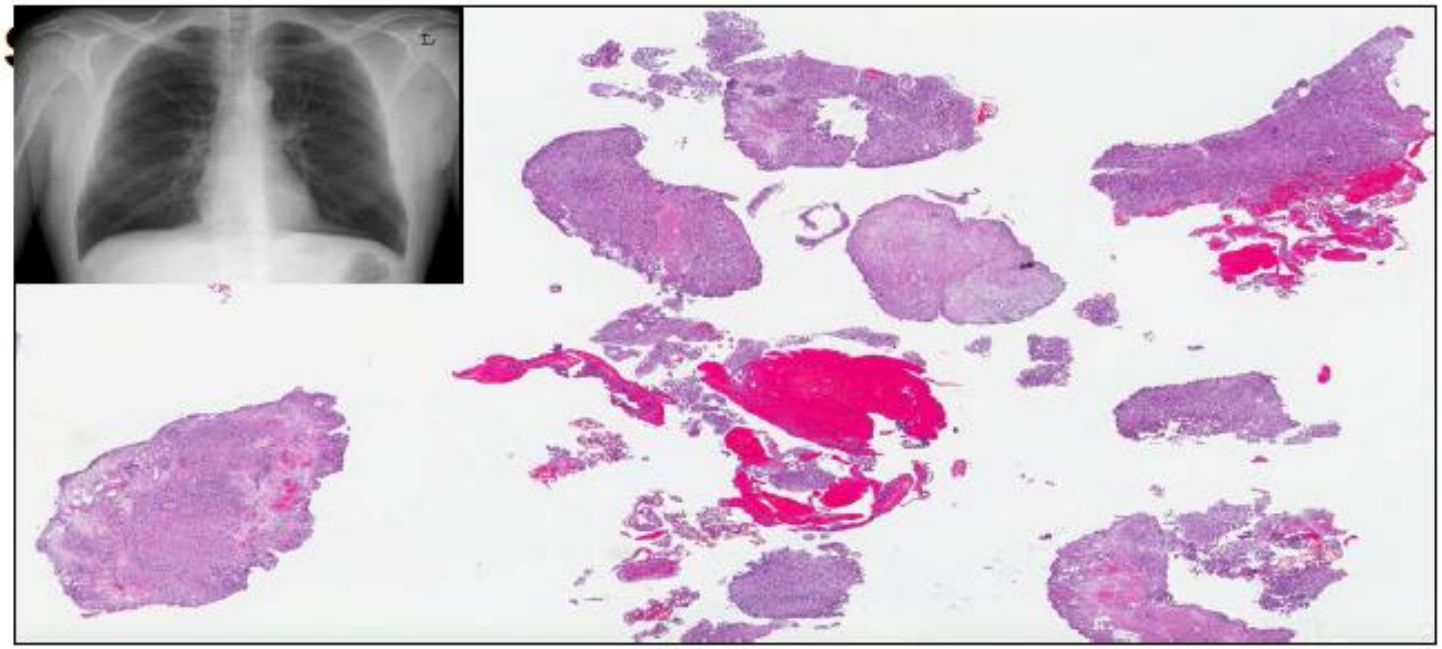
doi: 10.1097/PAP.0000000000000264

This Talk – Unusual Suspects

- Case Studies
    - Image as a Proxy? – ER^+ Breast Cancer
    - Need for Clear Labels! - Tall Cell Variant of Pap. Thyroid Cancer
    - Wild West of Subtyping - Sarcomas
    - In-situ Imaging of Omics!- Prostate Cancer
- Closing Arguments

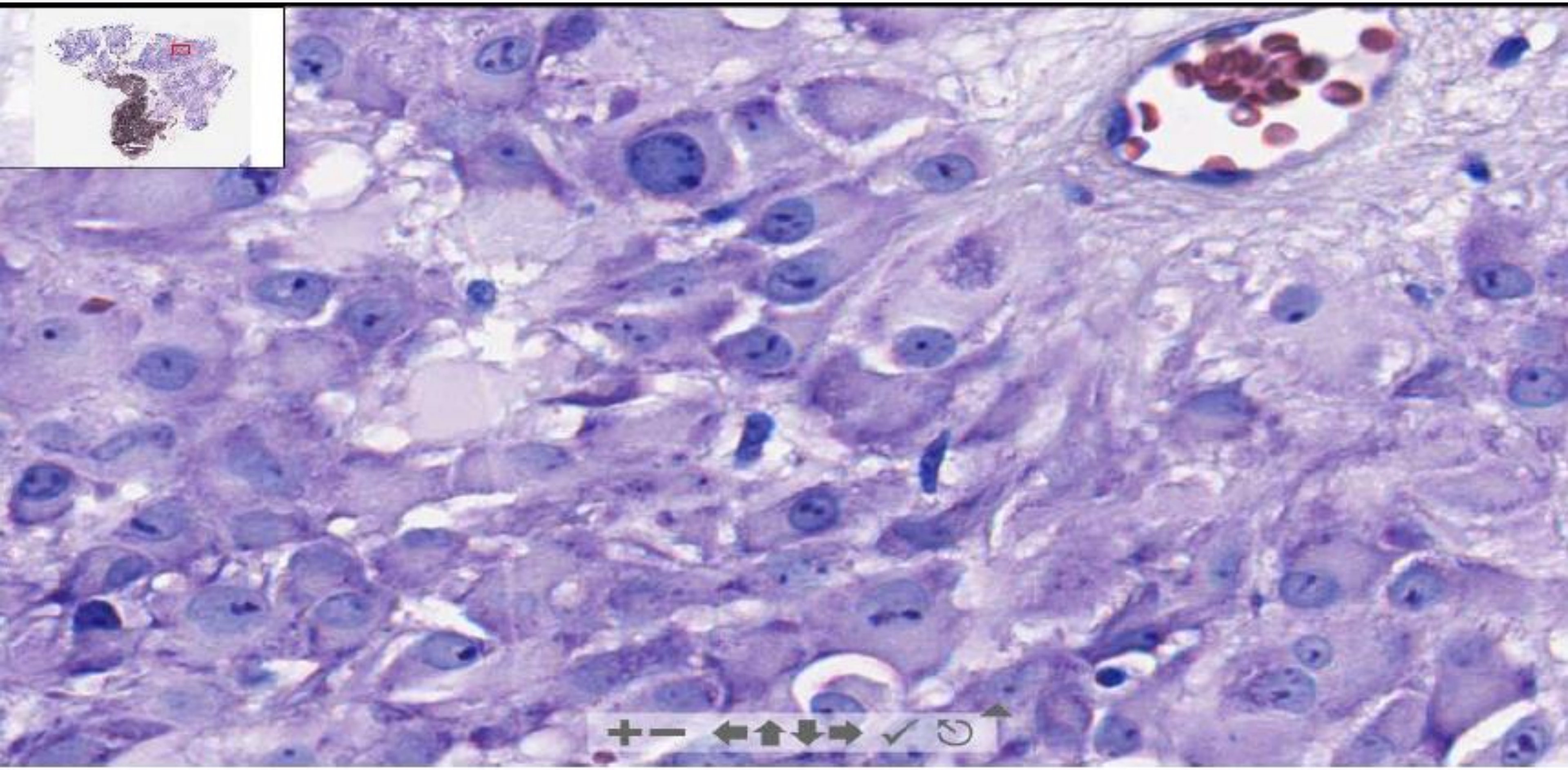

Whole Slide Images

Sheer Size



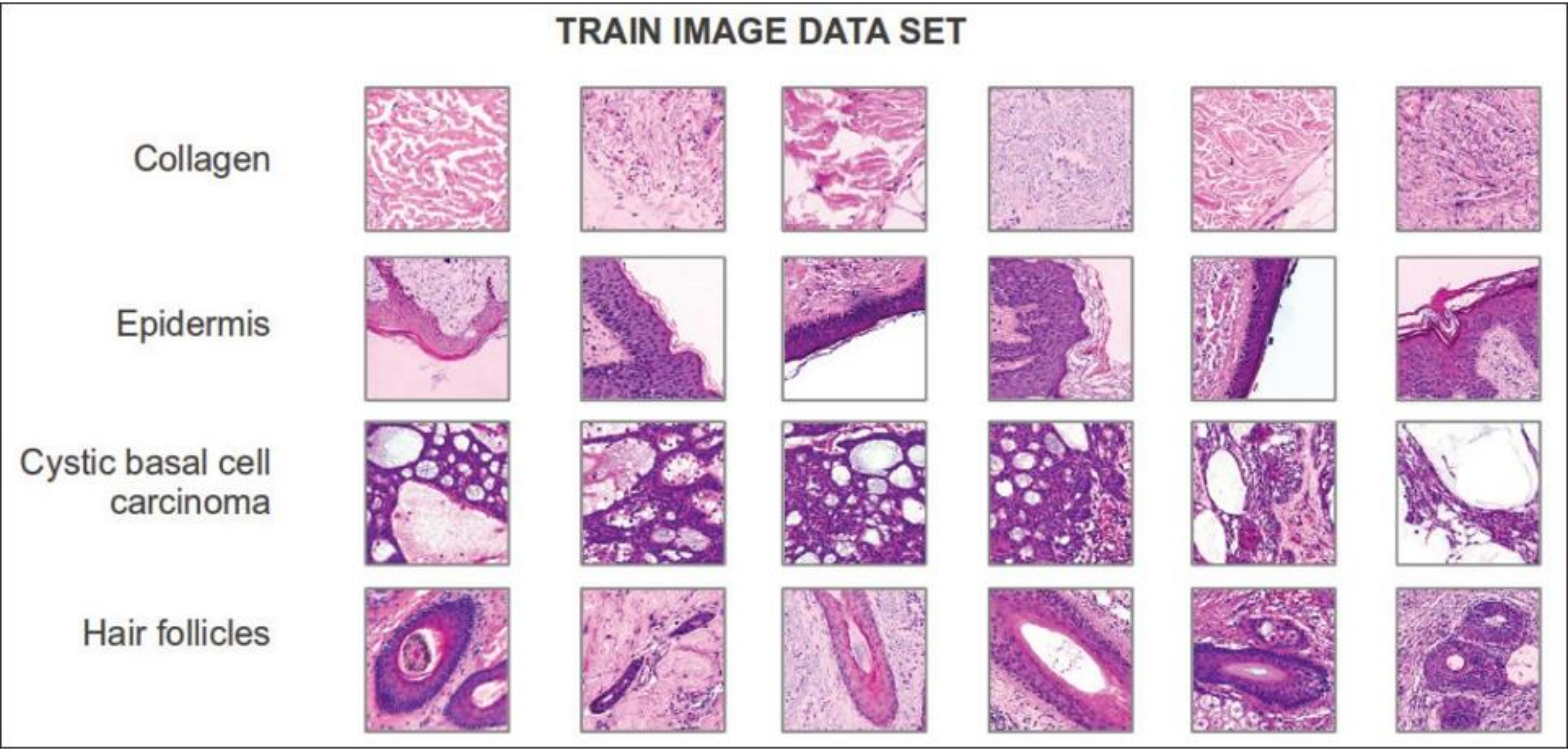
In terms of total pixel-normalized display in the same field of view, a 2k x 2k pixel digital radiographic chest X-ray image (A) is dwarfed when compared to a 40x scan of a typical 2.5 x 2.0 cm biopsy (654Mb with 20:1 loss compression).

Sheer Variety - Variability



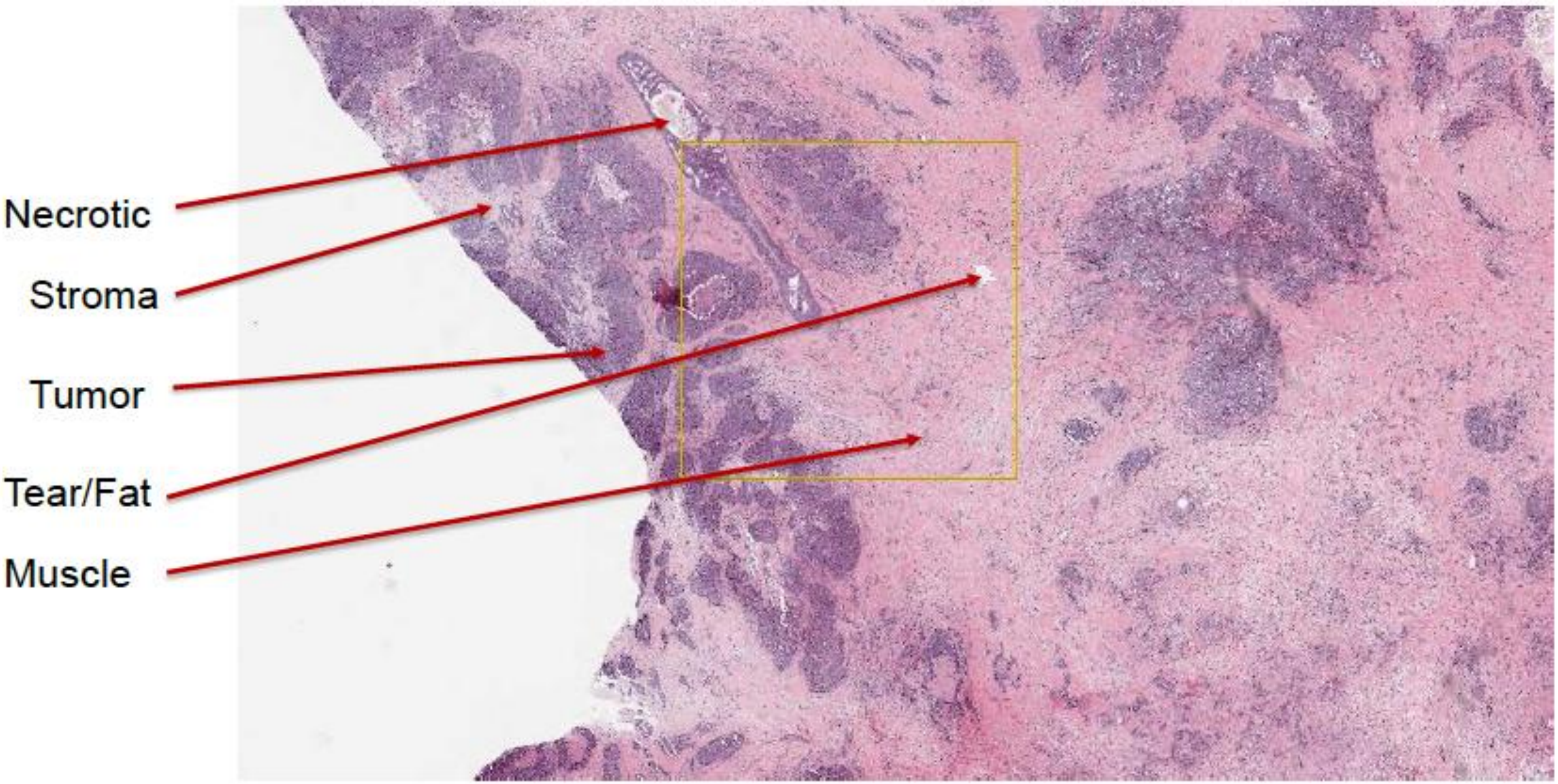
Variability within & across WSIs & over all subjects

Sheer Variety - Types



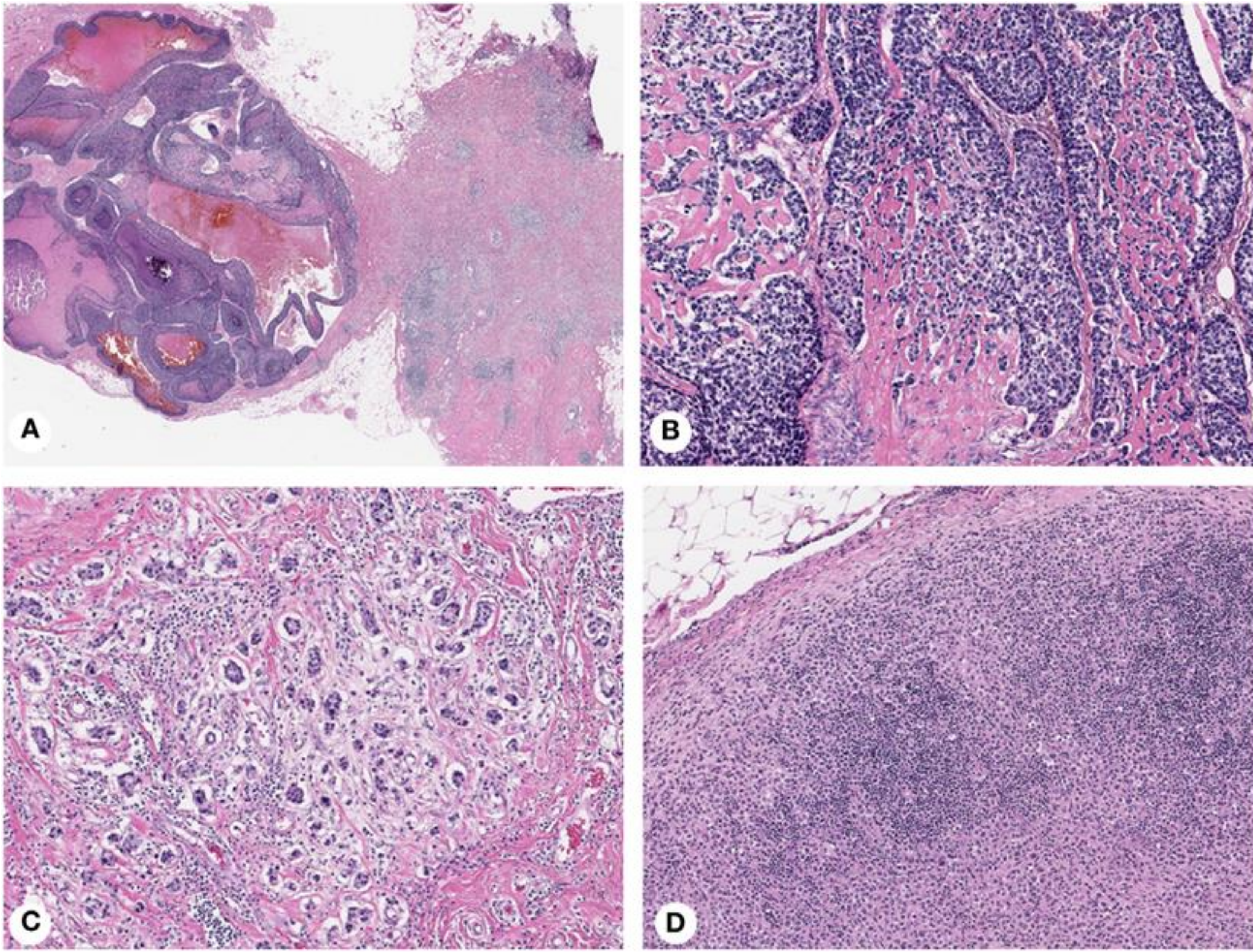
Variation in Features and Organization!

Sheer Variety – State & Tissue Type



Tissue compartments within WSI of different types & in different states

Histologic (Molecular/Outcome) Heterogeneity



BIAS IN PATHOLOGY SCORING

Name	Brief Description	Source, y
Visual traps		
Illusion of size[a]	Perception of an object's size is influenced by the context in which it is displayed; it has further been shown that this perception is influenced by memory and other stimuli	Conway et al,[5] 2008; Whiting et al,[18] 2004; Pannucci and Wilkins,[19] 2010
Craik-O'Brien-Cornsweet illusion[a]	Perception of brightness (or staining intensity) of an object or surface is solely determined by the brightness of its edge or interface and not the brightness of the entire surface	Plodowski and Jackson,[22] 2001; McClain et al,[23] 2014; Kurki et al,[24] 2009
Checker shadow illusion[a]	Perception of a surface's brightness is influenced by our knowledge of how it should appear, even if it is covered by a shadow; this perception ignores variations at the edges of shadows but recognizes those associated with sharp color changes at edges	Purves et al,[25] 1999; Masuda et al,[26] 2014
Distinguishing colors and hues[a]	Perception of colors and hues depends on their context; more are recognized if they are presented as a gradient rather than in isolation	Various; see text
Lateral inhibition[a]	Tendency for activated neurons to influence neighboring neurons in the visual pathway, yielding an increased ability to respond to edges of surfaces	Cao and Shevell,[37] 2005; Devinck and Spillmann,[38] 2009
Inattentional blindness	Phenomenon of failing to observe salient features or events when engaged in a different task	Devinck et al,[39] 2006; Kingdom,[41] 2014
Cognitive traps		
Confirmation bias[a]	Predisposition of people to seek information supportive of a favored hypothesis	Memmert,[43] 2006
Diagnostic drift[a]	Situation in which scoring values vary slightly and in a consistent fashion during the course of a study	Cross,[7] 1998; Crissman et al,[8] 2004
Anchoring	Predisposition to rely too heavily on the first information presented (the so-called anchor); also known as tunnel vision or fixation error	Drew et al,[44] 2013; Rouse et al,[48] 2015; Burkhardt et al,[49] 2011
Search satisfaction	Tendency to stop searching for a diagnosis once one event confirms an opinion, even if more events are available for evaluation	Fandel et al,[54] 2008; Fleck et al,[55] 2010; Craig et al,[56] 2016
Context bias[a]	Predisposition to consider a sample as abnormal when viewed in series with other samples showing a high disease prevalence but not when the sample is interpreted as part of a group with lower disease prevalence	Allred et al,[15] 1998; Berbaum et al,[59] 2015
Avoidance of extreme ranges[a]	Tendency to avoid extremes of ranges when assigning pathology scores	Cross,[7] 1998
Number preference[a]	Predisposition to assign numerical scores ending in 0 or 5	Morris,[66] 1994; Cai and Li,[68] 2015; Pickering,[70] 1992
Gambler's fallacy[a]	Inability to consider individual samples and endpoints (eg, cytoplasmic versus membrane staining) as events independent from previous and following slides or scoring events	Crawford et al,[76] 2015; Viray et al,[77] 2013

BIAS IN PATHOLOGY SCORING WITH WSIs?

Name	Brief Description	Source, y
Visual traps		
Illusion of size[a]	Perception of an object's size is influenced by the context in which it is displayed; it has further been shown that this perception is influenced by memory and other stimuli	Conway et al,[5] 2008; Whiting et al,[18] 2004; Pannucci and Wilkins,[19] 2010
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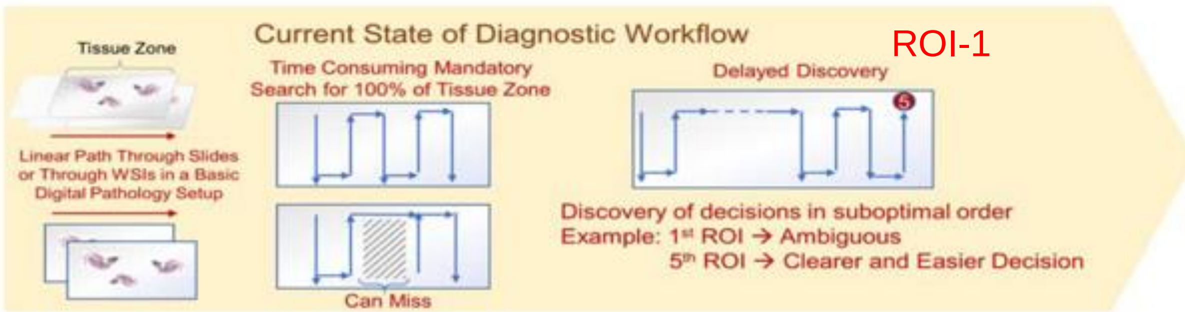
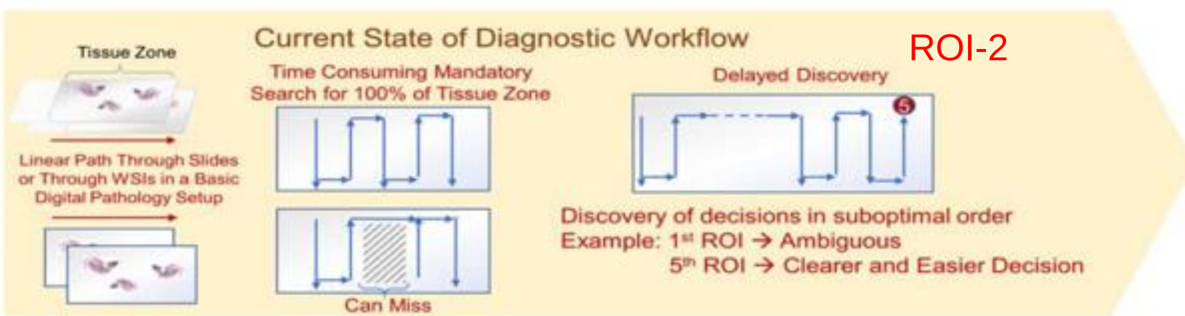
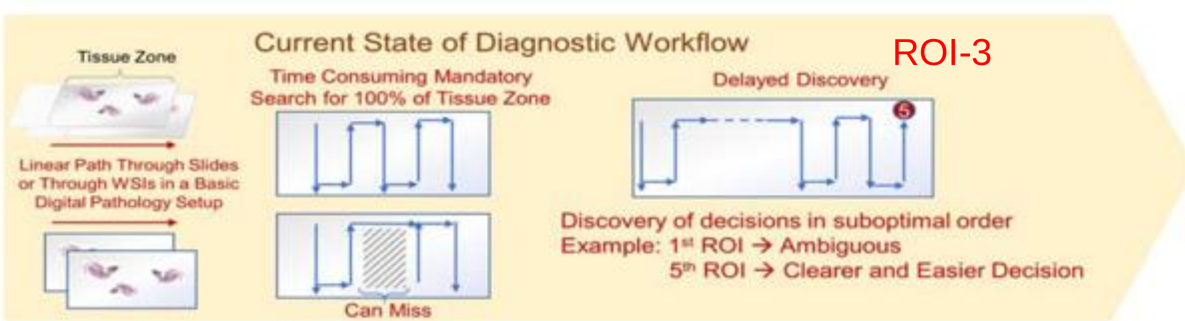
Use Case I – Image as a proxy for molecular markers



ROI-1



ROI-2

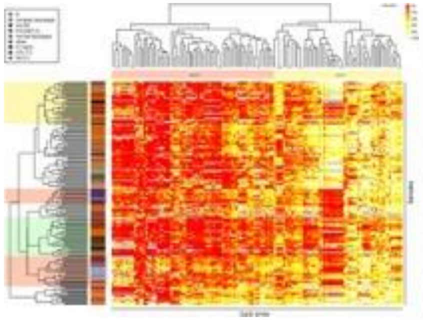


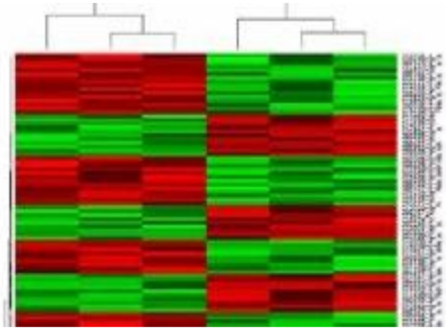
ROI-3

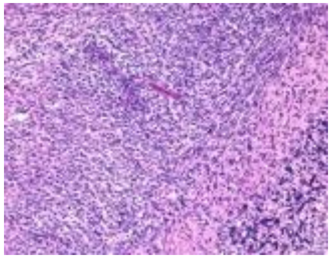
Multiple tasks

Biomarkers

Clinical
Biopsy







Biomarkers

Patient Stratification
Survival?

Onco*type* DX® Genes

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

INVASION

Stromelysin 3
Cathepsin L2

HER2

GRB7
HER2

GSTM1

CD68

BAG1

ESTROGEN

ER
PGR
BCL2
SCUBE2

REFERENCE

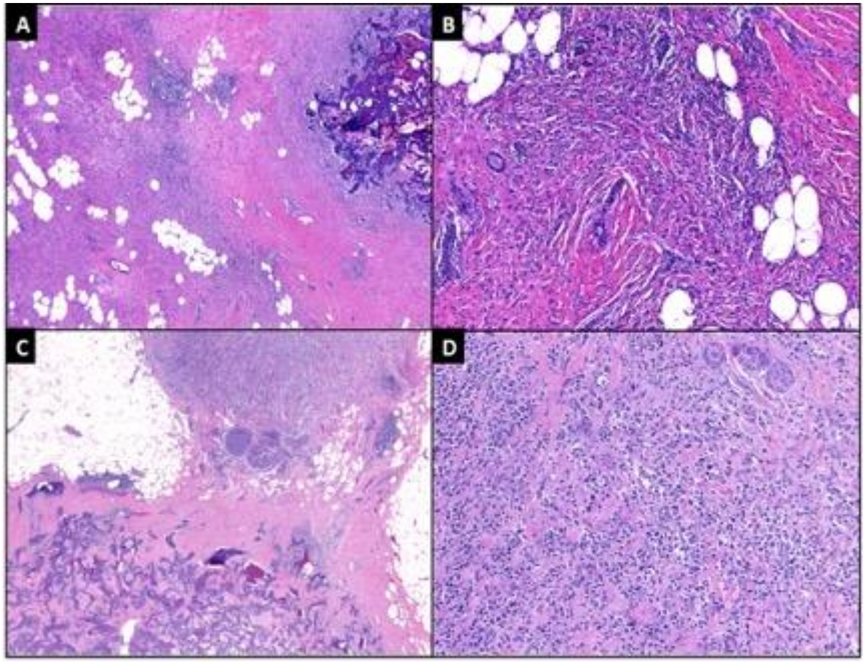
Beta-actin
GAPDH
RPLPO
GUS
TFRC

Paik et al. N Engl J Med. 2004;351:2817-2826

Recurrence Score

RS (unscaled) =

+ *0.47 x HER2* group score
– 0.34 x ER group score
+ 1.04 x proliferation group score
+ 0.1 x invasion group score
+ 0.05 x CD68
– 0.08 x GSTM1
– 0.07 x BAG1



Representative images of two classical invasive lobular carcinoma cases with Oncotype DX RS > 30

Comparison of Oncotype DX With Modified Magee Equation Recurrence Scores in Low-Grade Invasive Carcinoma of Breast

Yanjun Hou, MD, PhD,[1] Debra L. Zynger, MD,[1] Xiaoxian Li, MD, PhD,[2] and Zaibo Li, MD, PhD[1]

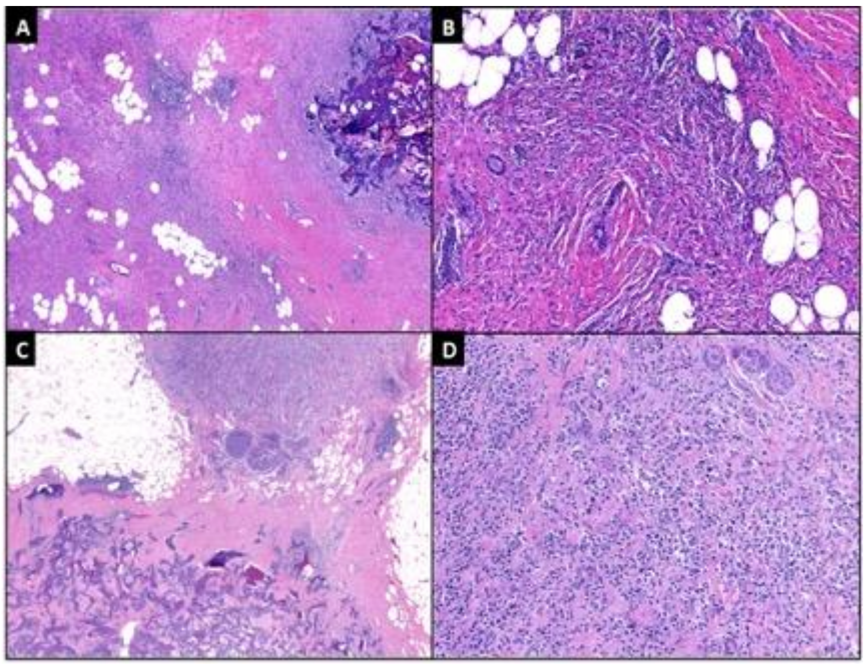
From the [1]Department of Pathology, Wexner Medical Center at The Ohio State University, Columbus, and [2]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA.

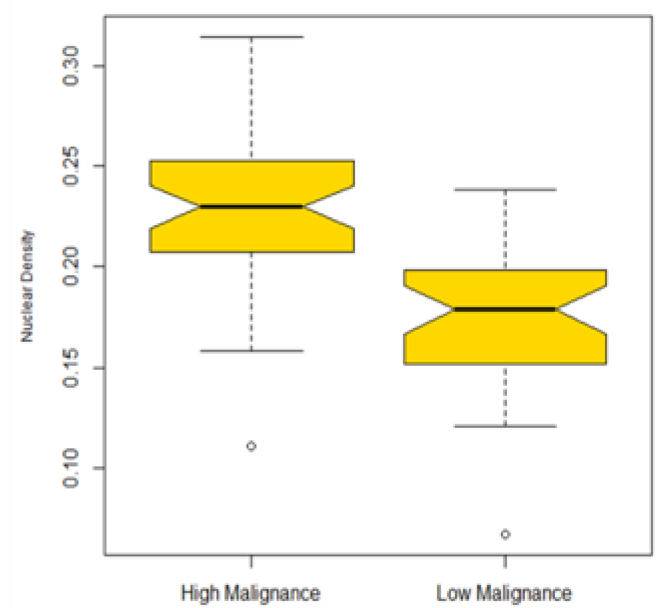
Key Words: Breast cancer; Lobular; Mucinous; Tubular; Magee equation; Oncotype DX; Recurrence score

CME

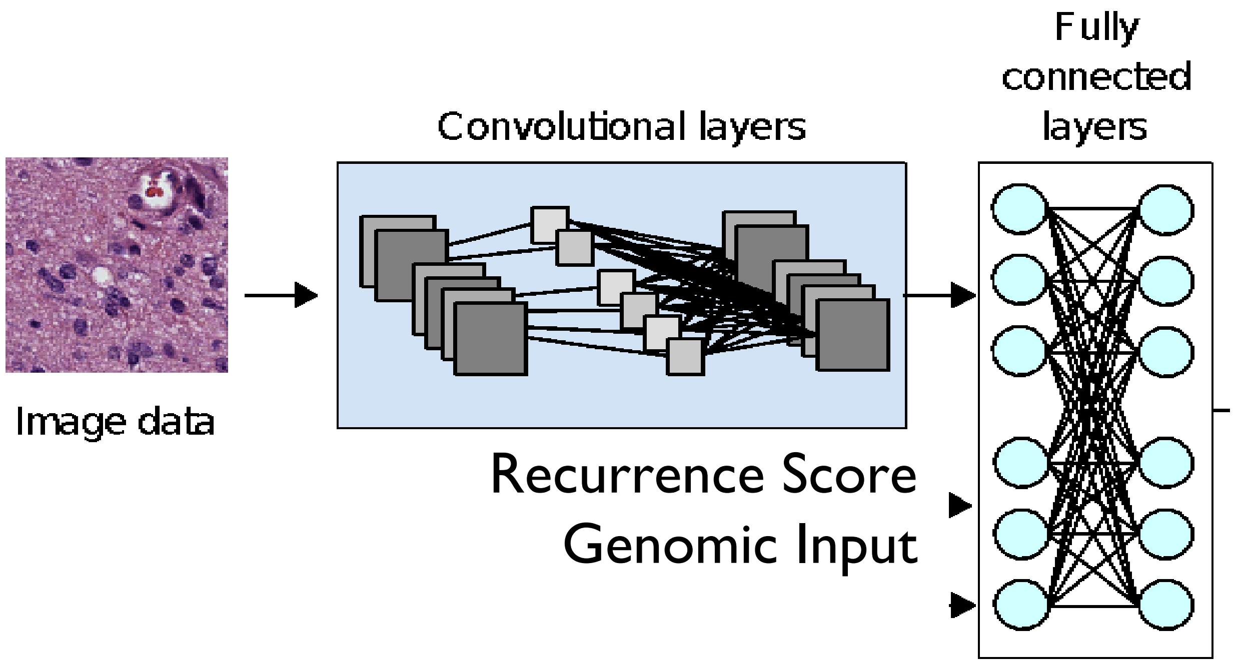
Recurrence Score & Images

Which image features best correlate with different different ranges?

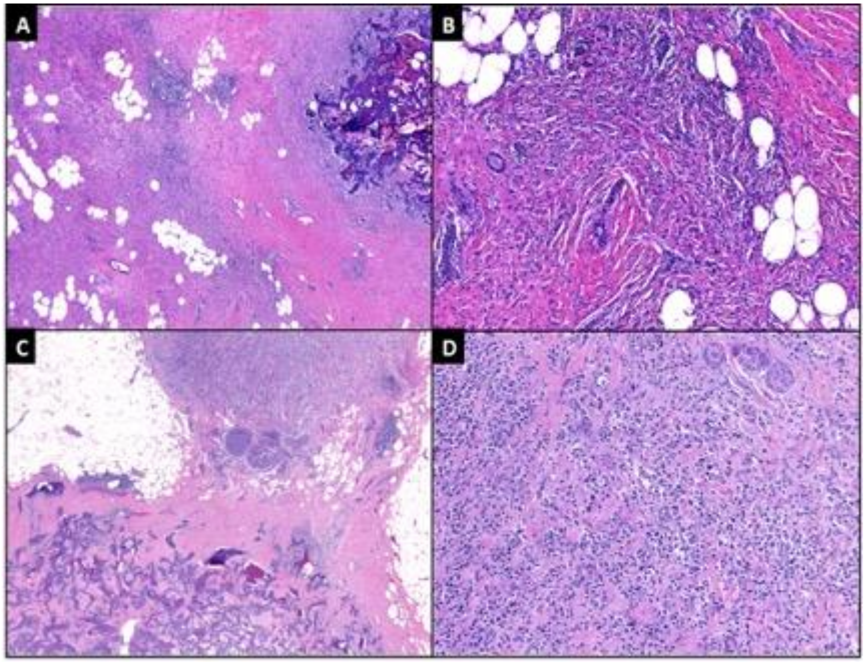




Creating a Morphological Proxy



Using grading criteria used in the clinic



Representative images of two classical invasive lobular carcinoma cases with Oncotype DX RS > 30

Parameter	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Absent*	Moderate	Marked
Mitotic count**	<9	9-17	>17

Final score	3 4 5	6 7	8 9
	Grade I	Grade II	Grade III

AJCC - Nottingham Score

Nottingham grading score

Parameter	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Absent*	Moderate	Marked
Mitotic count**	<9	9-17	>17

Final score	3	4	5	6	7	8	9
	Grade I			Grade II		Grade III	

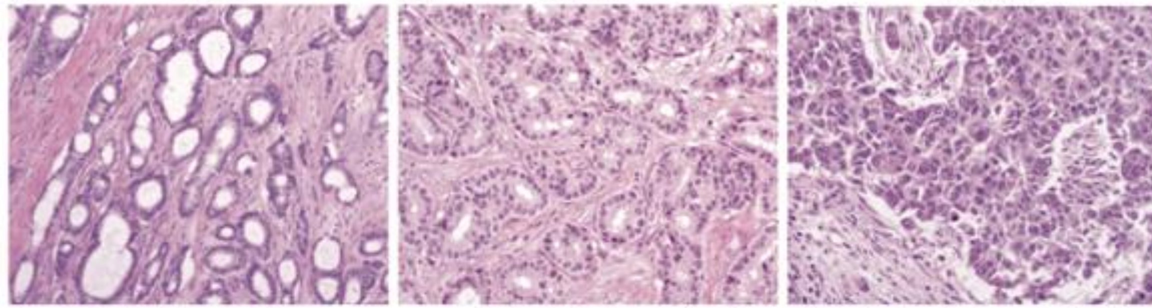
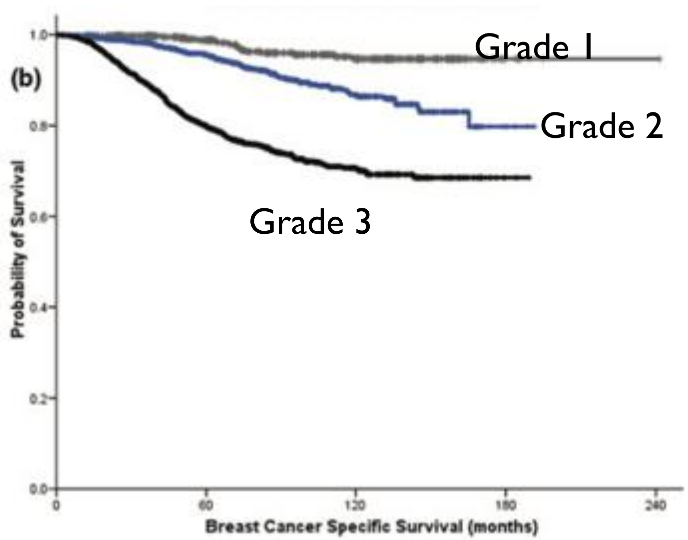


Figure 1. Histological grade of breast cancer as assessed by the Nottingham Grading System. (a) A well-differentiated tumor (grade 1) that demonstrates high homology to the normal breast terminal duct lobular unit, tubule formation (>75%), a mild degree of nuclear pleomorphism, and low mitotic count. **(b)** A moderately differentiated tumor (grade 2). **(c)** A poorly differentiated (grade 3) tumor with a marked degree of cellular pleomorphism and frequent mitoses and no tubule formation (<10%).

AJCC - Nottingham Score

DOI: [10.1186/bcr2607](https://doi.org/10.1186/bcr2607)



Annotation Protocol for ER+ Breast Cancer per the Nottingham Score

Parameter	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Absent*	Moderate	Marked
Mitotic count**	<9	9-17	>17

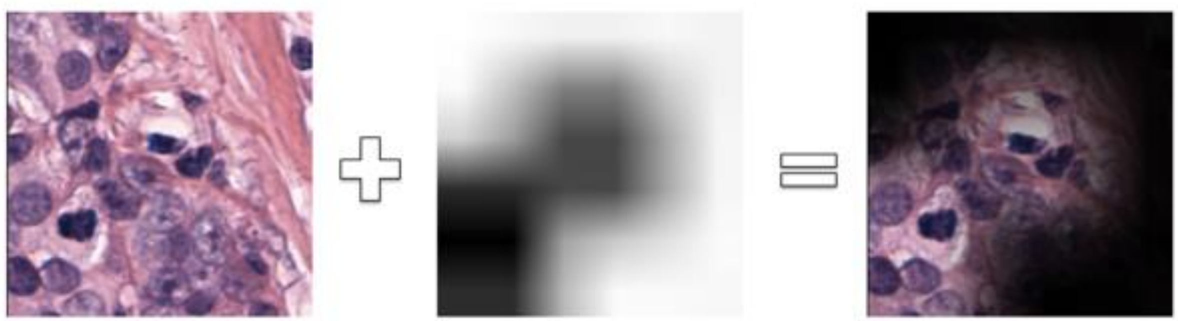
Final score	3	4	5	6	7	8	9
	Grade I			Grade II		Grade III	

Perform on a Whole Slide Image

1. At magnification of 2x
    a. Task: Identify and outline tumor region
    Tool: Line
2. At magnification of 4x
    a. Task: Annotate regions of tubule formation and record score
    Tool: Line
        i. Score 1: more than 75% of the whole carcinoma forms acini
        ii. Score 2: 10-75% of the whole carcinoma forms acini
        iii. Score 3: less than 10% of the whole carcinoma forms acini
3. At magnification of at least 20x
    a. Task: Measure nuclei of benign ductal epithelial cells
    Tool: Line
        i. Use for baseline of normal cell to then identify nuclear pleomorphisms
    b. Task: Annotate 0.52mm x 0.52mm regions and score based on mitotic activity
    Tool: Rectangle
        i. Score 1: 0-7 per 10 high-power field (0.52mm)
        ii. Score 2: 8-15 per 10 high-power field (0.52mm)
        iii. Score 3: greater than 16 per 10 high-power field (0.52mm)
    c. Task: Annotate 0.52mm x 0.52mm regions and score based on nuclear pleomorphisms
    Tool: Rectangle
        i. Score 1: nuclei only slightly larger than benign breast epithelium (< 1.5 × normal area
        ii. Score 2: nuclei distinctly enlarged (1.5–2 × normal area) often vesicular, nucleoli visible
        iii. Score 3: markedly enlarged vesicular nuclei (> 2 × normal area), nucleoli often prominent

Attention based techniques - Relevance

Identify the disease “relevant” regions capturing state



Mitosis mixed with normal cells and other tissues

CNN mask identifying “relevant” regions

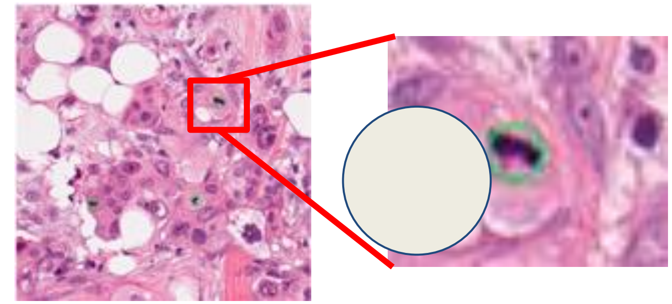
ONLY mitosis highlighted

(~82% Accuracy, precision, recall and F-score and verified by pathologists)

Mitosis Datasets

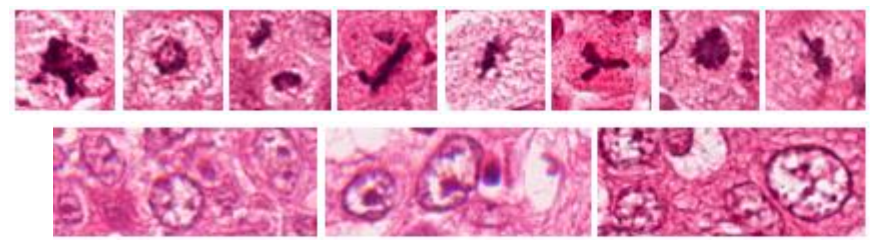
TUPAC16

- 73 breast cancer cases
- ×40 magnification
- Annotated



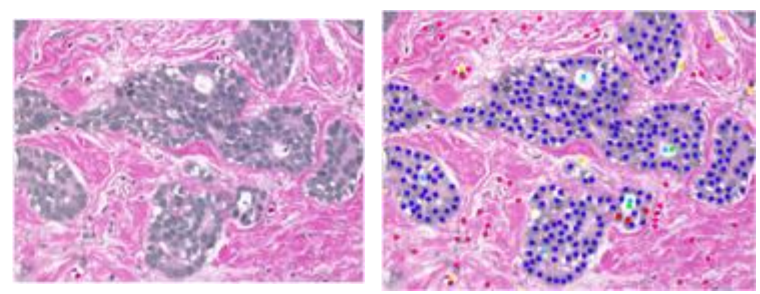
MITOS
ATYPiA_14

- Breast Cancer: Mitosis: #749
- Different magnification level: x40,x20,x10
- Breast Cancer: Atypia

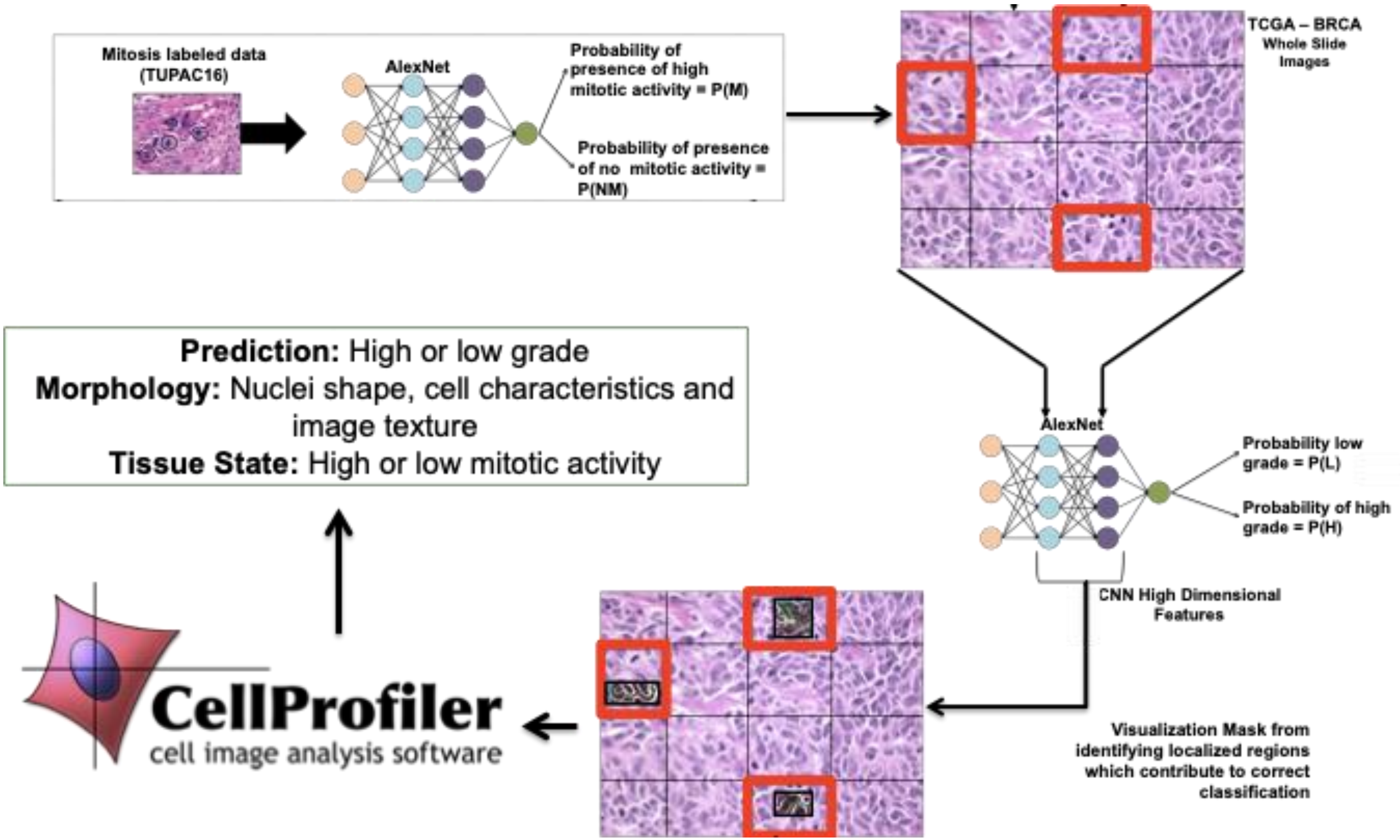


BreCaHAD19

- Mitosis: #115
- Apoptosis: #271
- Tumor nuclei: #20155
- Non-tumor nuclei: #1905



The Framework

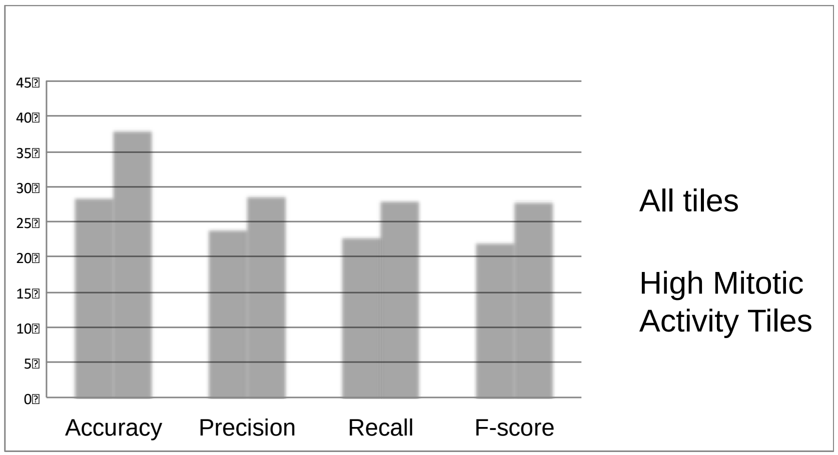


The Framework

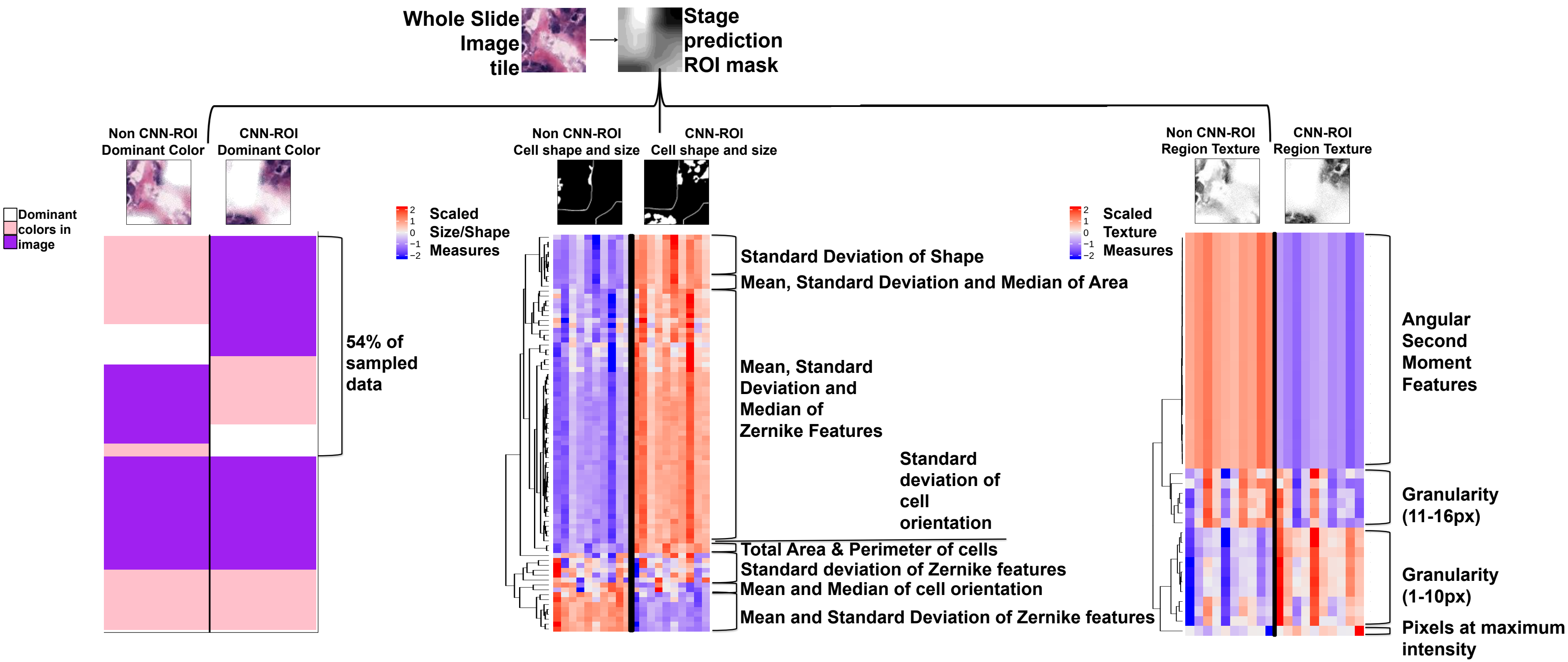
Deep learning pipelines that importance *samples input* and *interprets output*

1. Pre-select regions of the image that are "relevant" to the disease
2. Process the regions for recognition of state
3. Predict the regions and label tumor/normal and subtypes
4. Confirm that these correspond with correct RS range and pick features that predict in RS-range
5. Repeat for better prediction/prognosis

Enhanced Model Prediction



Interpreted CNN predictions



Work in Progress

- Collect training data of all parameters

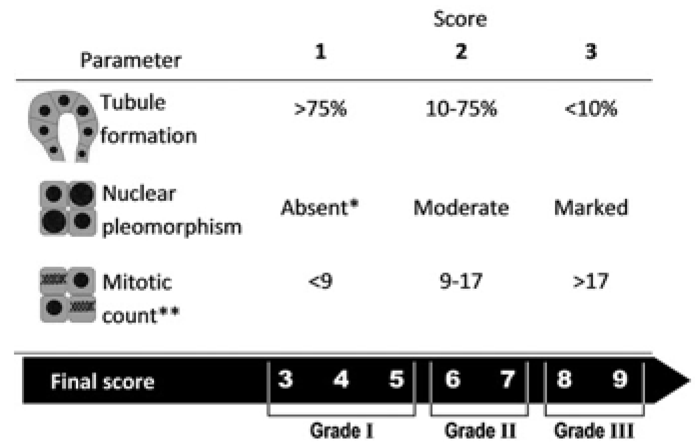
- More attention-based learning

- Process patch and images at different resolutions

- Refine multi-task learning

- Leverage Un/Semi-supervised learning

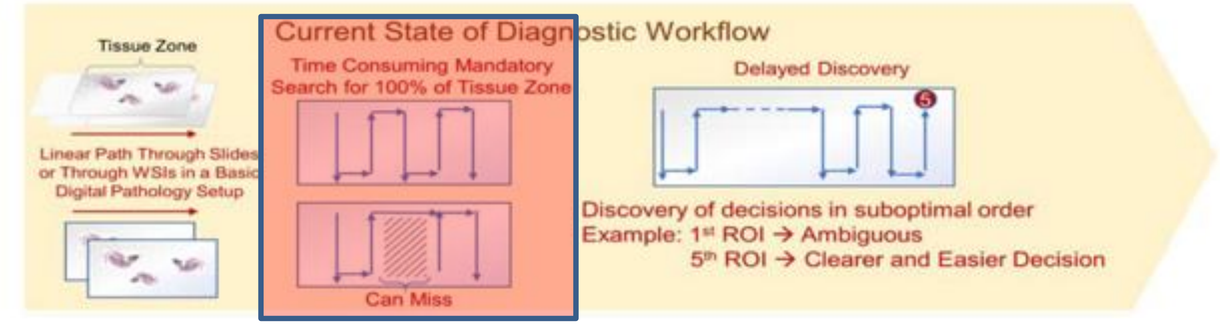
- Connect with Recurrent Score



Per Becich Survey

A: Very High; P: Medium; D: High

Use Case II – Few and Fuzzy labels



<u>Task well not defined</u>

Papillary thyroid carcinoma, tall cell variant:
tram-track pattern (H&E, ×40)

“Tall cell” Variant

- “Tall cell” variant diagnosis depends exclusively on histopathology
- Associated with <u>worse prognosis</u> among papillary thyroid cancer
- Should not definition of “tall cell” and “tall cell variant” be well established?
- <u>Well, no!</u>

1976

Tall cell variant first described

“Tall cell” H:W > 2:1

1976-2017

Obfuscation of “tall cell” and “tall cell variant” definition

“Tall cell” H:W ranged from > 2:1 to > 3:1 and a tumor percentage criterion introduced, which ranged from 30% to 70%

2017

4th Edition WHO classification

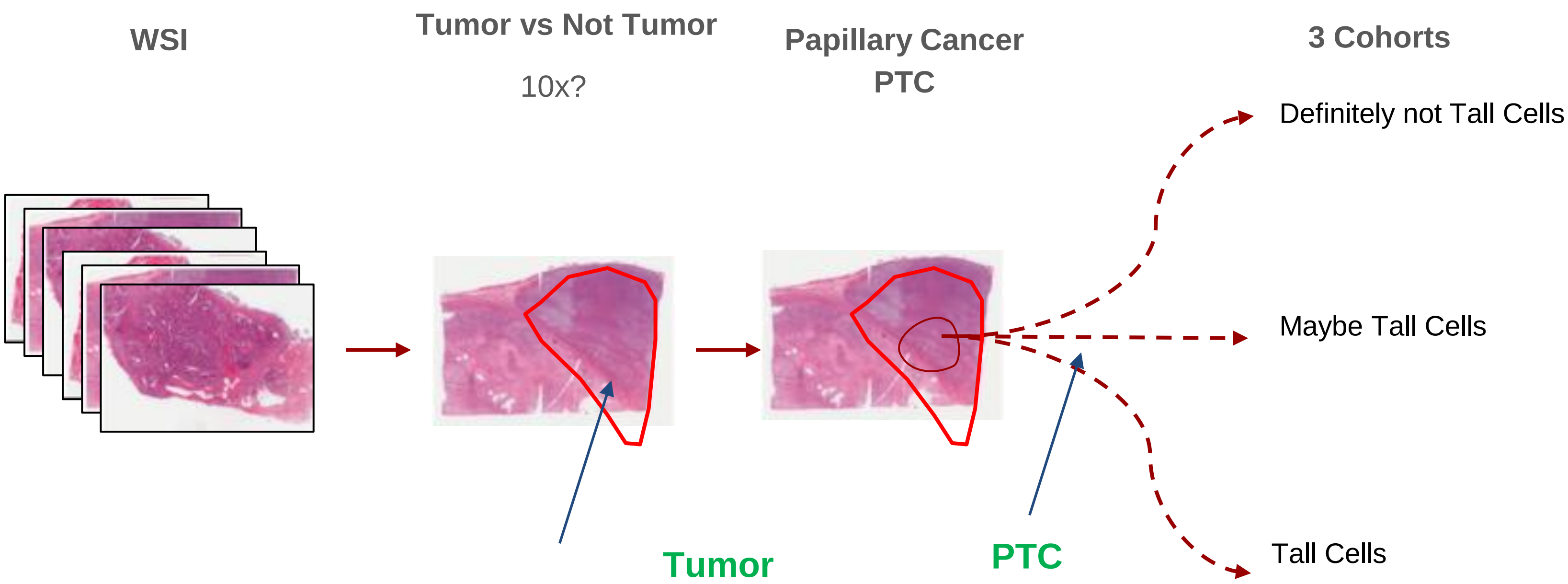
H:W between 2:1 and 3:1 and minimum tumor percentage criterion = 30%

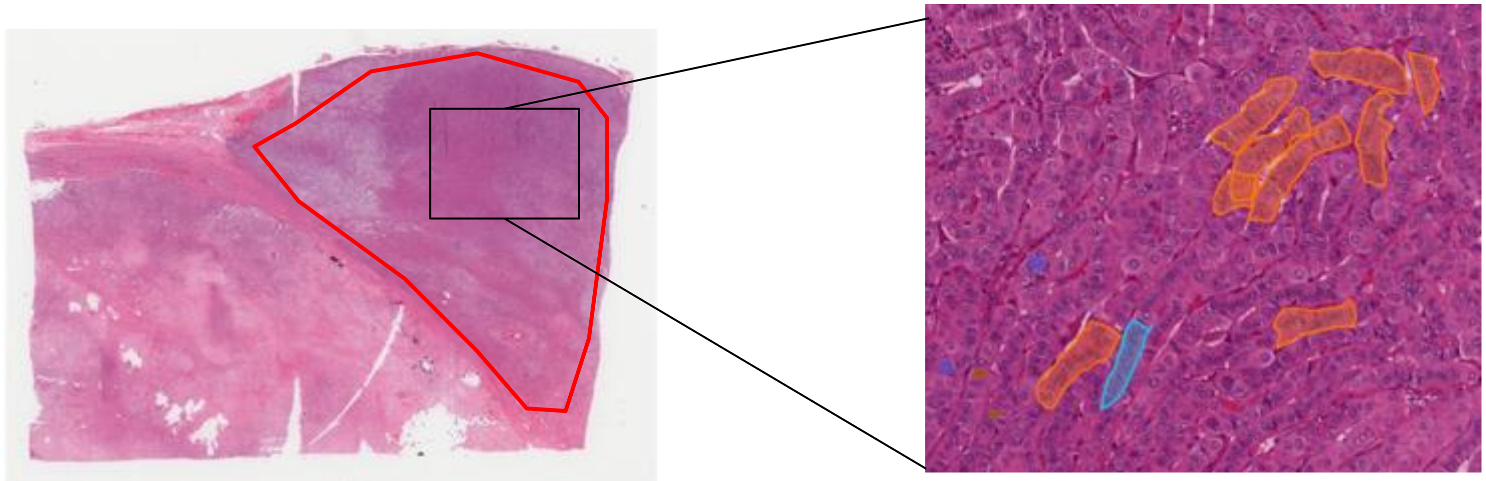
2017-present

Continued discord

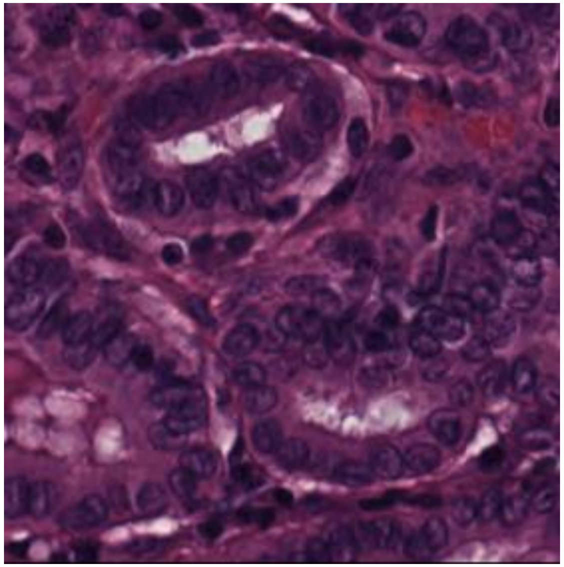
Tumor percentage criterion ranging from >10% to >50%
“Tall cell” determination highly prone to interobserver variability

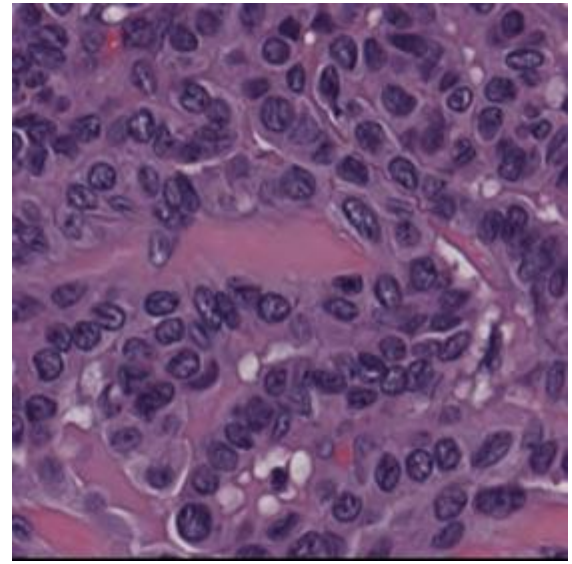
Annotation Plan



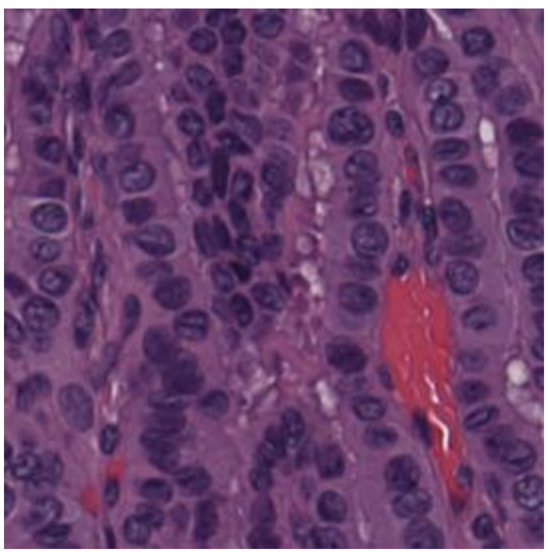


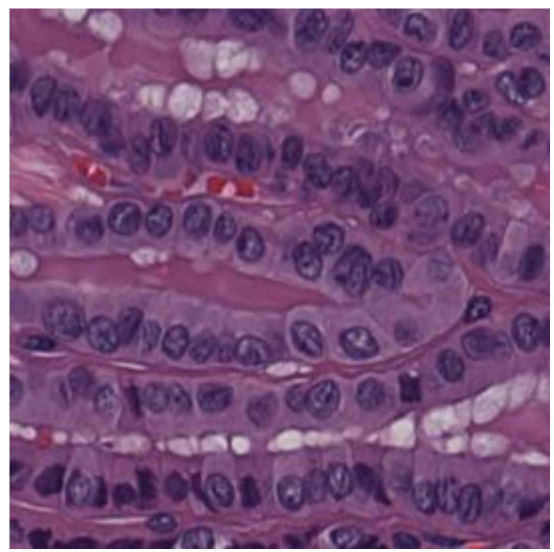
Not Tall Cell

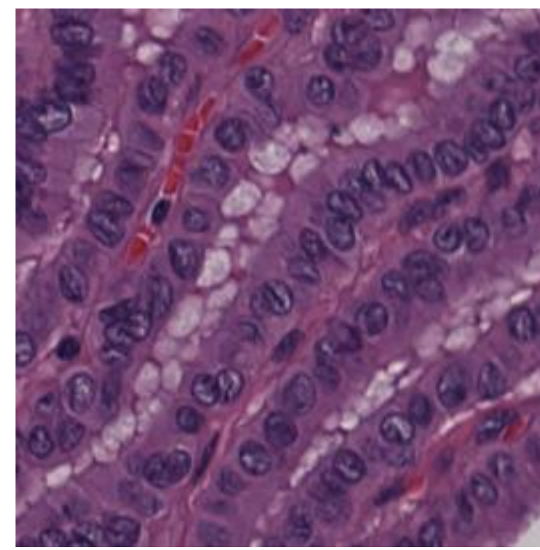




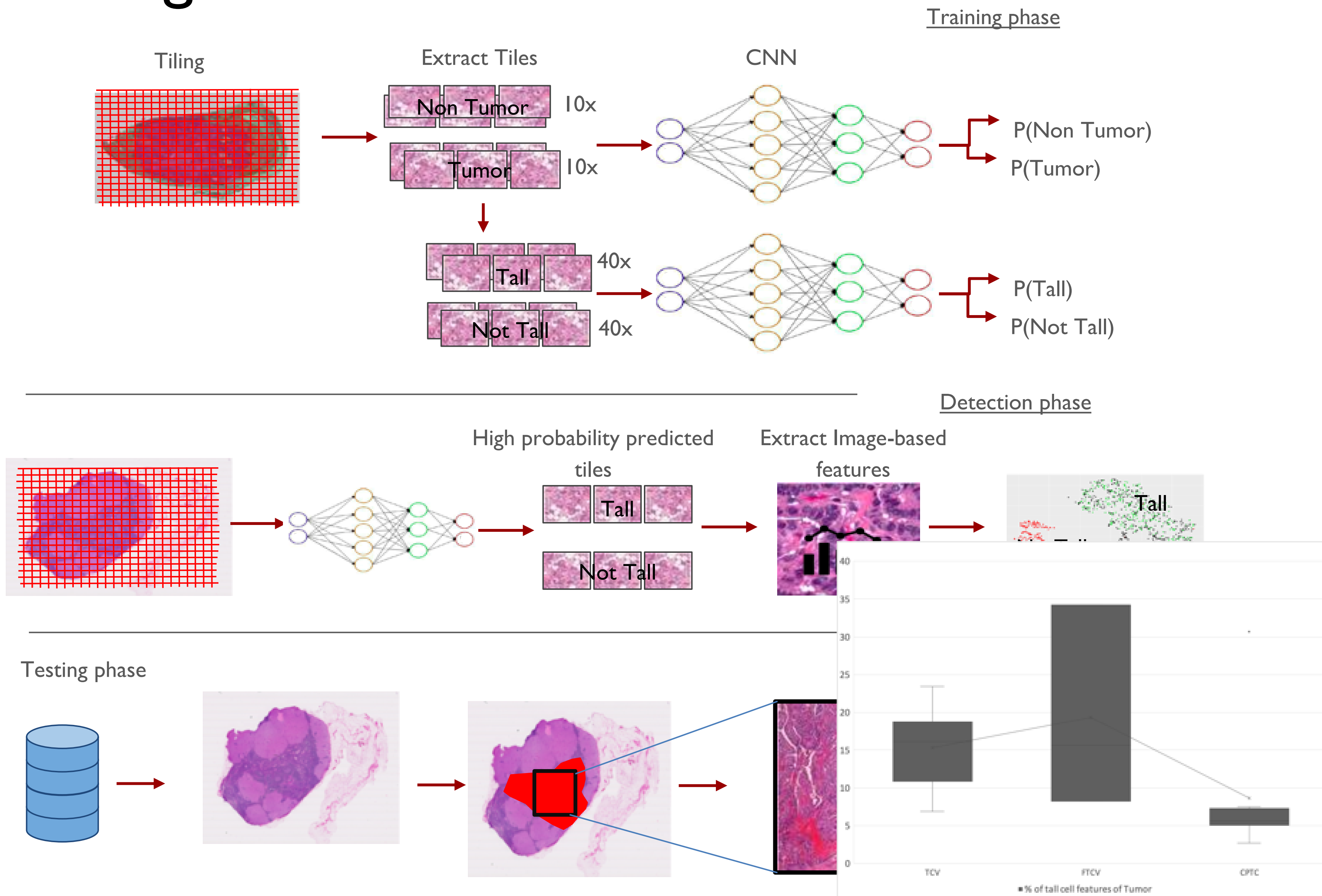
Tall Cell



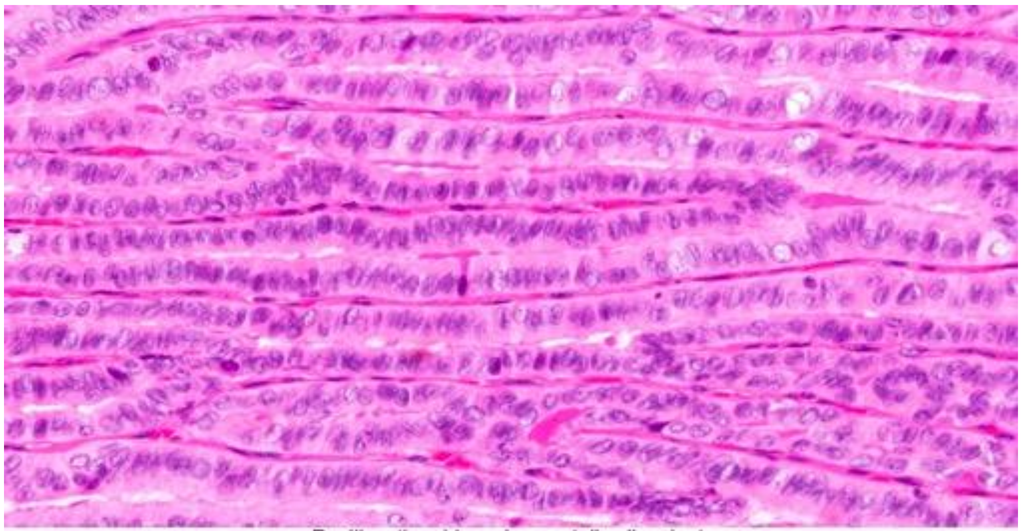




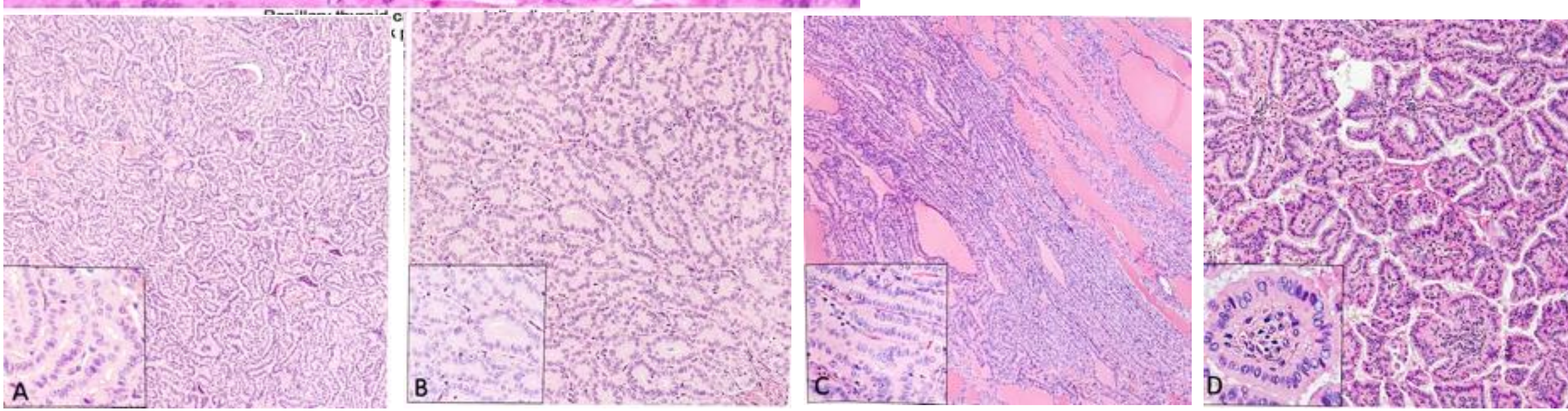
Finding Tall Cells



Going Forward – Tissue-specific Patterns

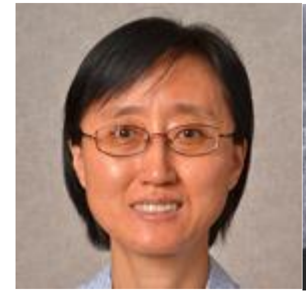


- Attention on features!
- Like Tall?
- Tram like patterns
- Domain knowledge helps!
- Data is a problem
- Not too many tall cells



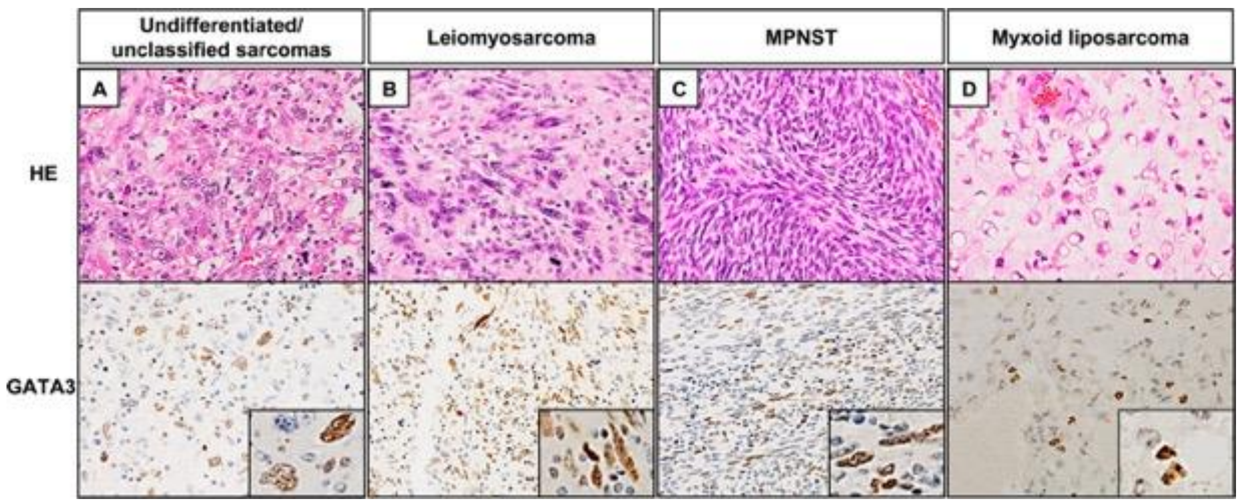
Per Becich Survey

A: Medium; P: Very High; D: Very High



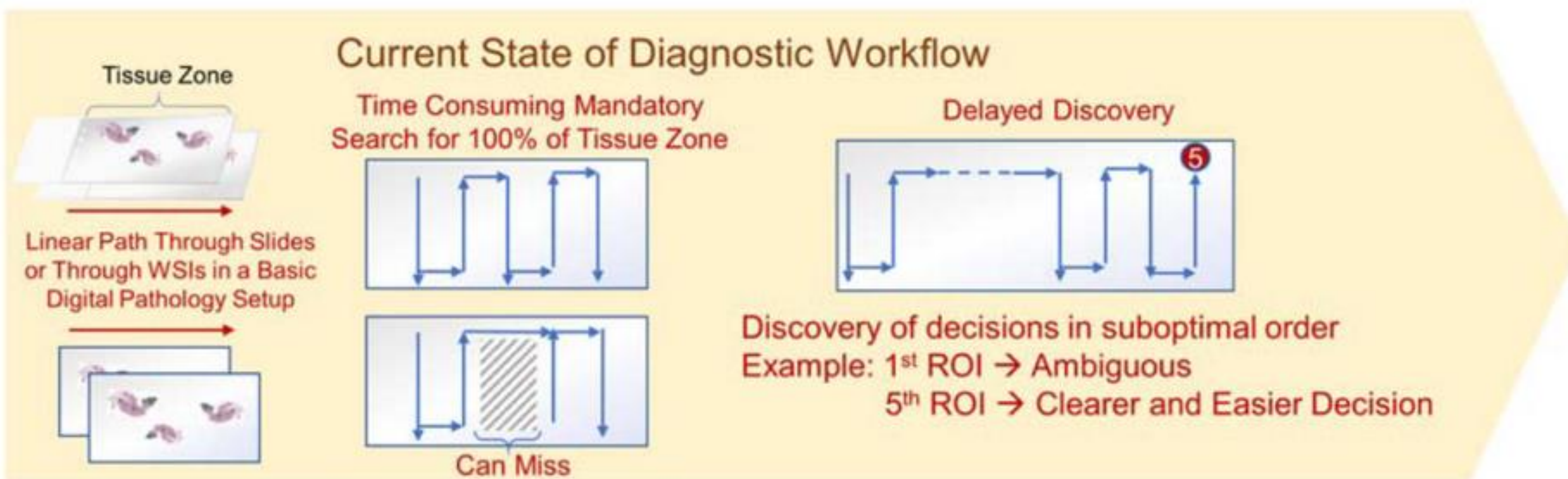
Dr. David Liebner   Dr. Xiaoyin Cui

Use case III – Too many subtypes and little data



The Goal: Genomic & Histopathologic Composite Grading System

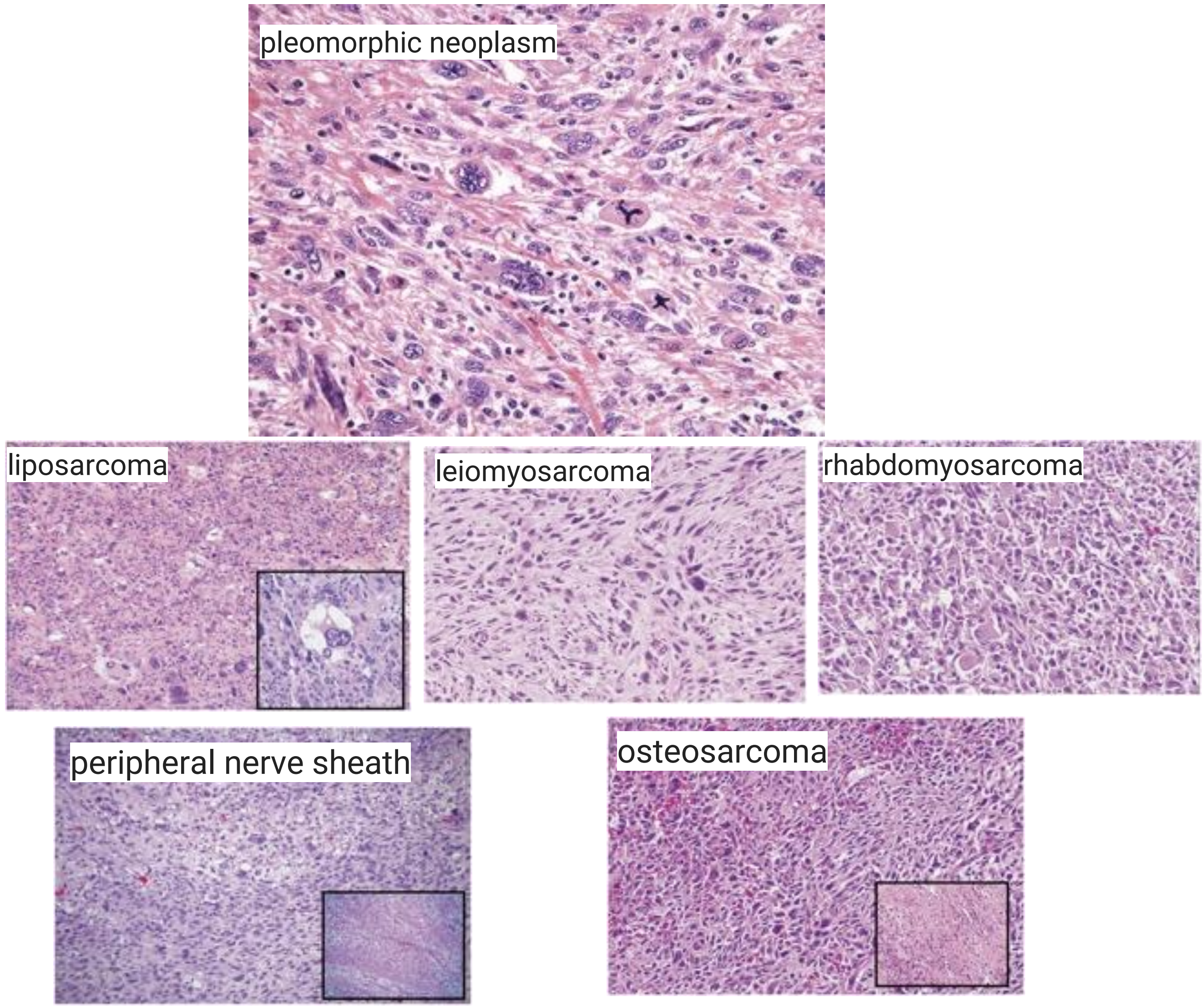
Use Case III: Few Definitions & Workflow



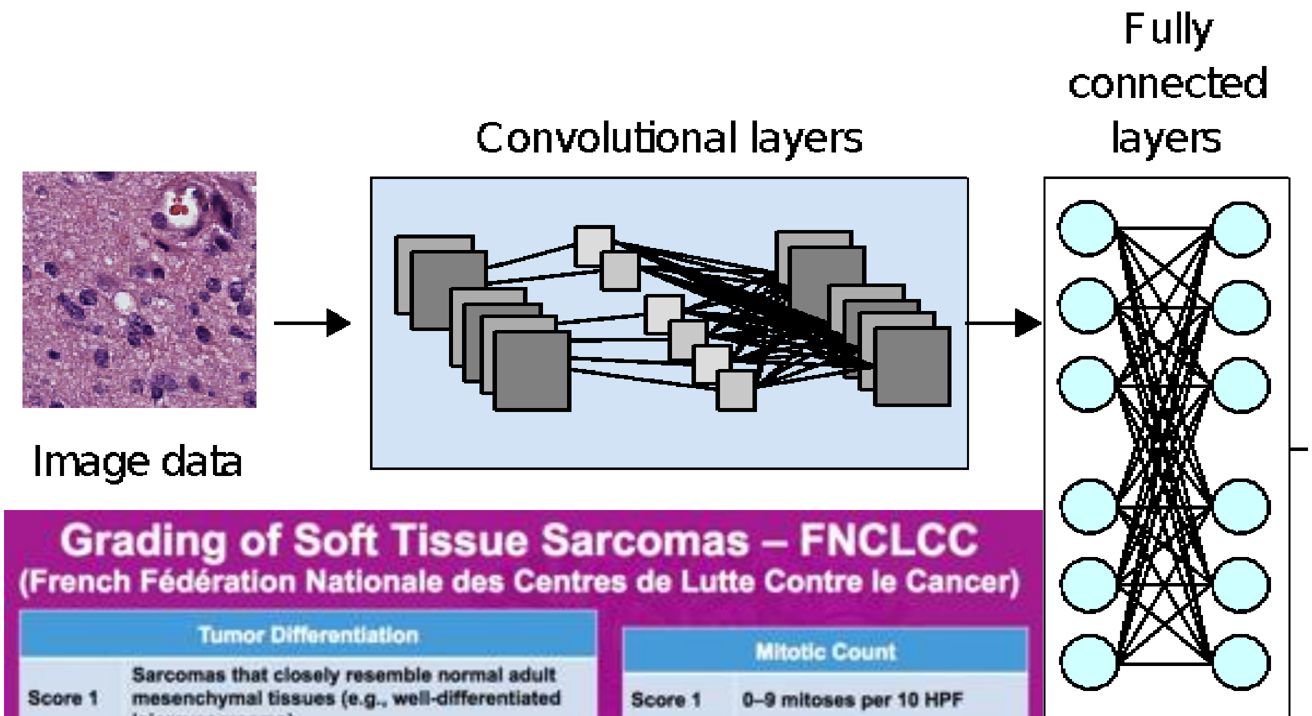
Consider This ...

https://www.nature.com/articles/modpathol2013174

An approach to pleomorphic sarcomas: can we subclassify, and does it matter?



Working w/ Grading



Grading of Soft Tissue Sarcomas – FNCLCC
(French Fédération Nationale des Centres de Lutte Contre le Cancer)

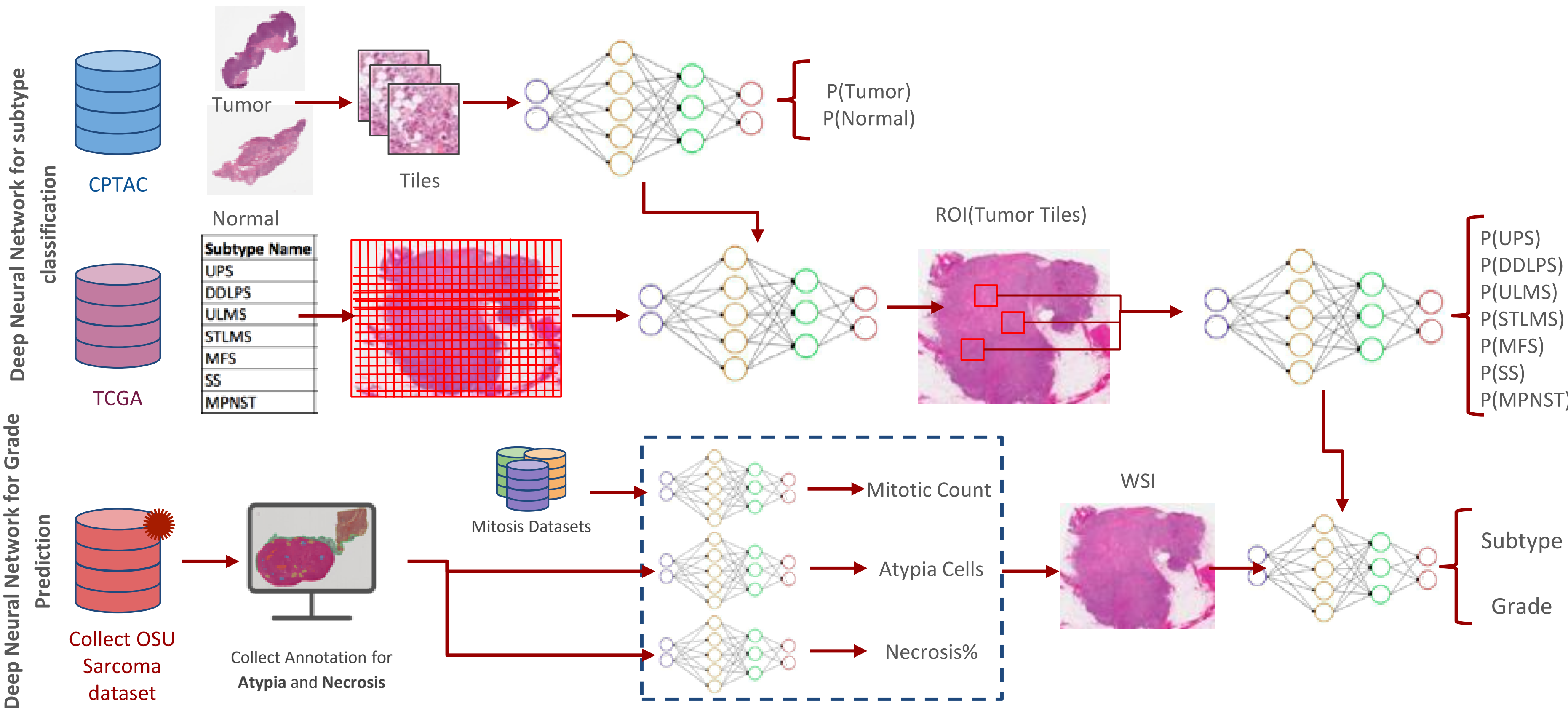
Tumor Differentiation	
Score 1	Sarcomas that closely resemble normal adult mesenchymal tissues (e.g., well-differentiated leiomyosarcoma)
Score 2	Sarcomas for which histologic typing is certain
Score 3	Embryonal and undifferentiated sarcomas, synovial sarcoma, and sarcomas of uncertain differentiation

Mitotic Count	
Score 1	0–9 mitoses per 10 HPF
Score 2	10–19 mitoses per 10 HPF
Score 3	≥20 mitoses per 10 HPF

Tumor Necrosis	
Score 1	No necrosis
Score 2	<50% tumor necrosis
Score 3	≥50% tumor necrosis

Histologic Grade (Differentiation + Mitotic Count + Necrosis)	
Grade 1 (low grade)	Total score: 2 or 3
Grade 2 (intermediate grade)	Total score: 4 or 5
Grade 3 (high grade)	Total score: 6, 7, or 8

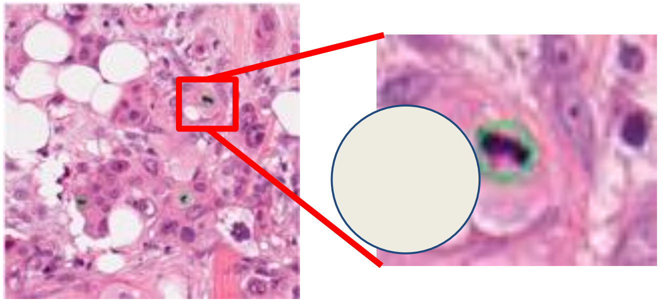
The Classification Task



Mitosis Datasets

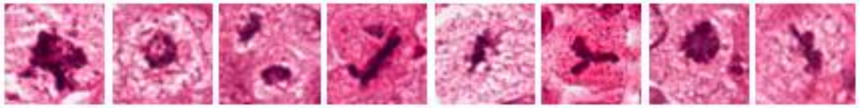
TUPAC16

- 73 breast cancer cases
- ×40 magnification
- Annotated



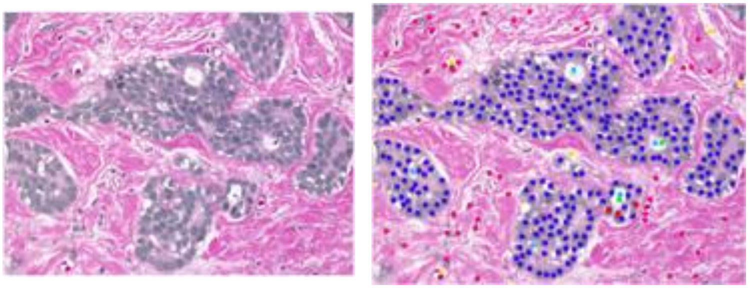
MITOS
ATYPiA_14

- Breast Cancer: Mitosis: #749
- Different magnification level: x40,x20,x10
- Breast Cancer: Atypia

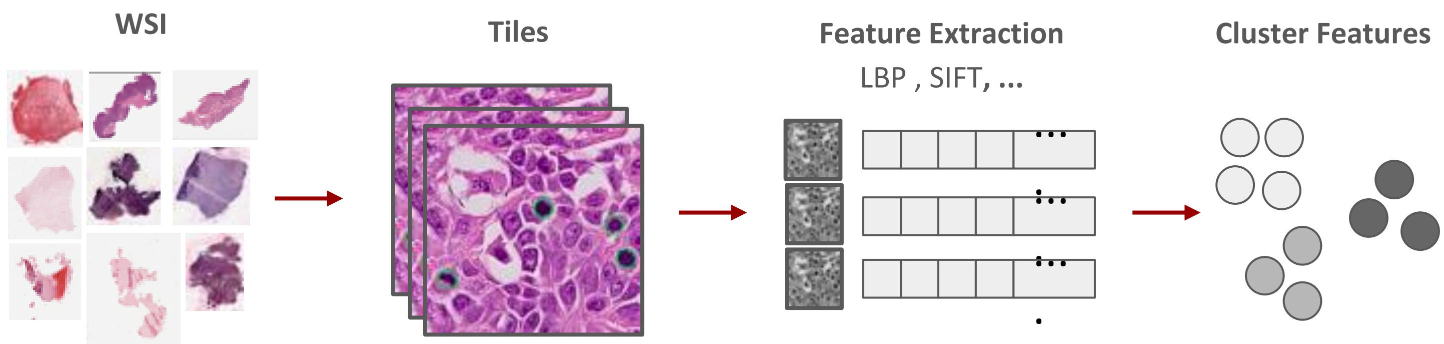


BreCaHAD19

- Mitosis: 115
- Apoptosis: 271
- Tumor nuclei: 20155
- Non-tumor nuclei: 1905



Unsupervised Learning



Variational Autoencoders

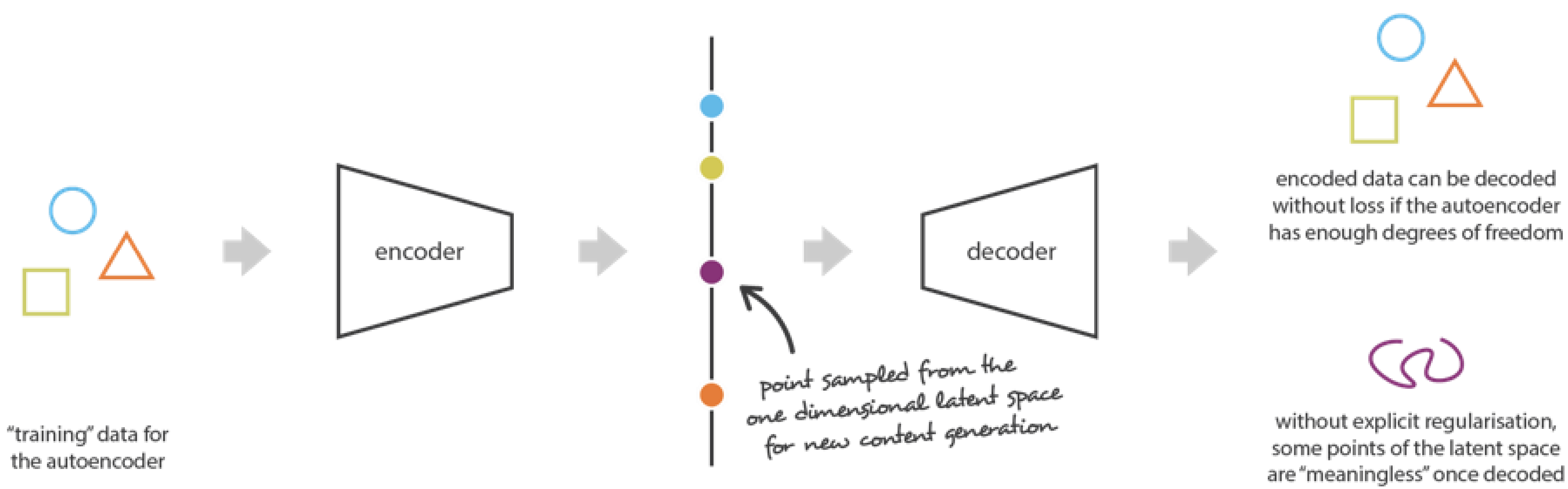


Table 2. Grading System for Cutaneous and Subcutaneous Soft Tissue Sarcoma in the Dog[a]

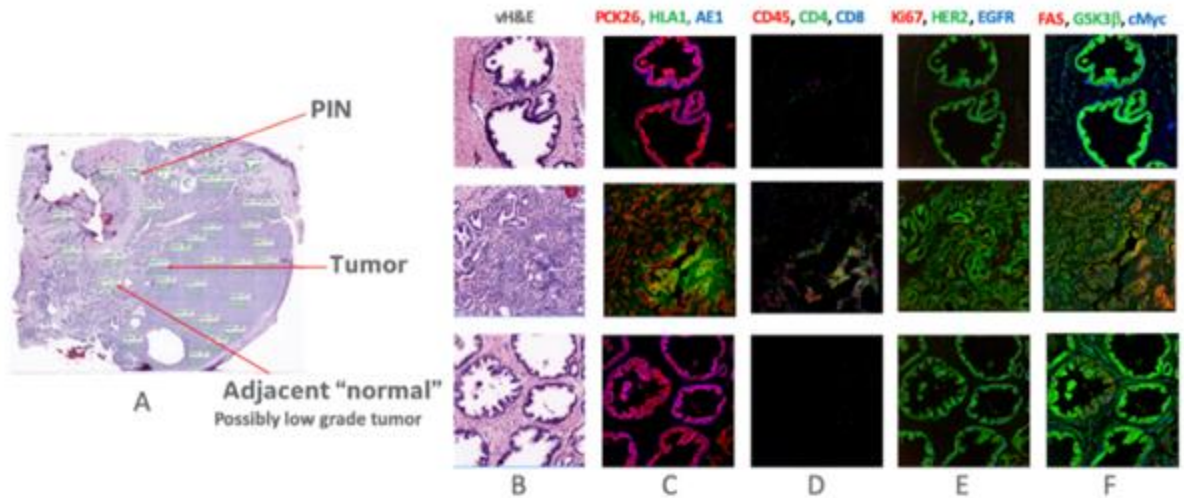
Differentiation score	
1	Sarcomas most closely resembling normal adult mesenchymal tissue, by type (eg, well-differentiated perivascular wall or peripheral nerve sheath tumors, well-differentiated fibrosarcomas, or well-differentiated liposarcomas)
2	Sarcomas for which histologic type can be determined, although differentiation is poor (eg, poorly differentiated liposarcoma, fibrosarcoma, poorly differentiated perivascular wall tumor or peripheral nerve sheath tumor)
3	Undifferentiated sarcomas, sarcomas of unknown type
Mitotic score: mitoses per 10 high-power fields (400×)	
1	0–9
2	10–19
3	> 19
Tumor necrosis score	
0	No necrosis
1	≤ 50% necrosis
2	> 50% necrosis
Histologic grade: total score[b]	
I	≤ 3
II	4–5
III	≥ 6

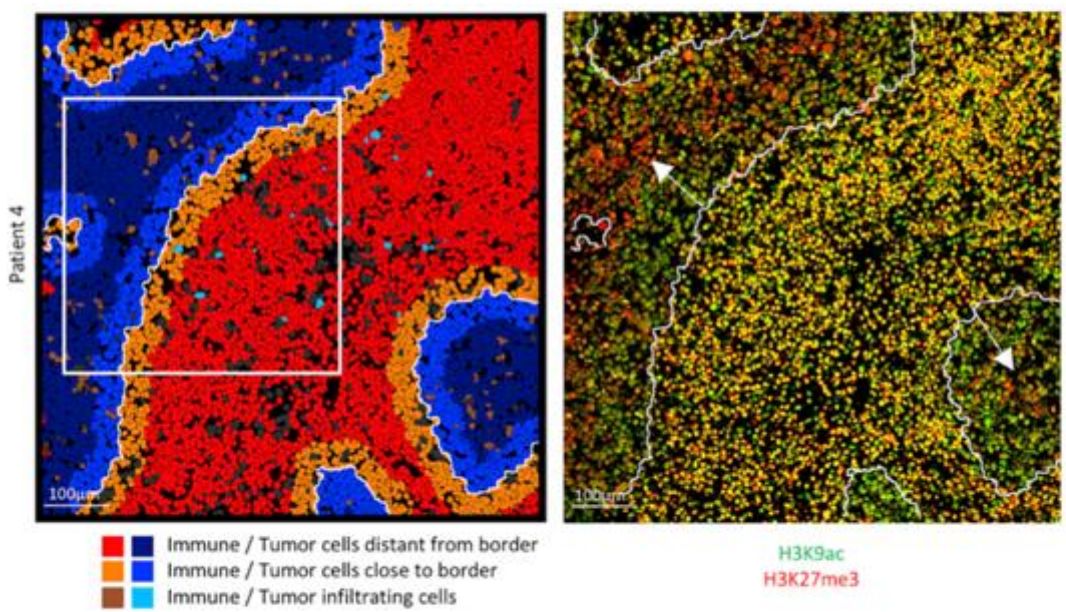
[a] From Trojani et al.[53]
[b] Combined differentiation, mitotic, and tumor necrosis scores.

Use Case IV- Multiplexed Single Cell Resolution

GE Global Research

P. Mallick
Stanford





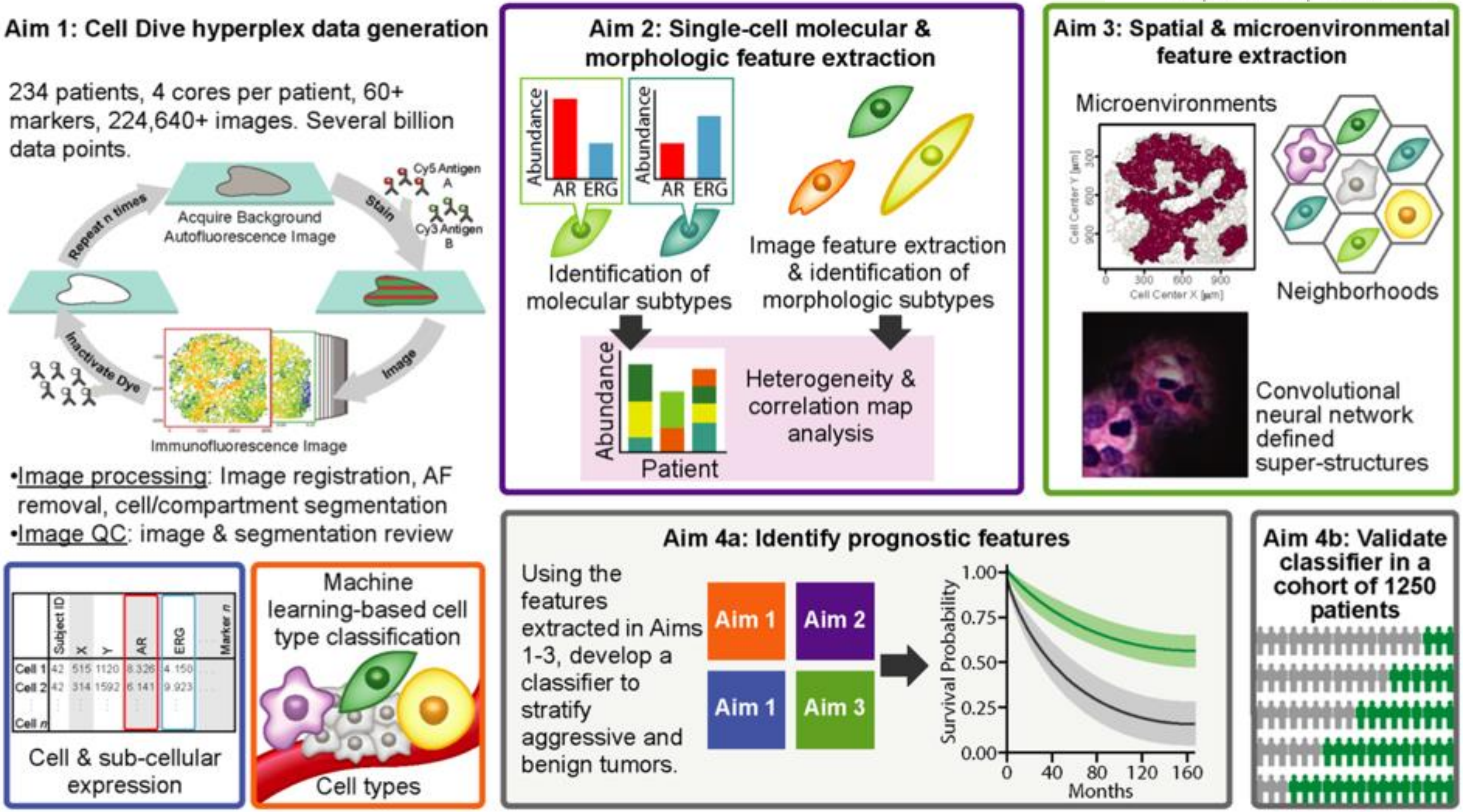
NATIONAL INSTITUTES OF HEALTH

Pathomics

GE Global Research

STANFORD SCHOOL OF MEDICINE

Stanford University Medical Center



Summary & Closing

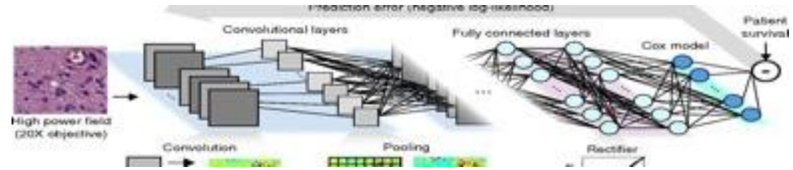
The Becich Survey

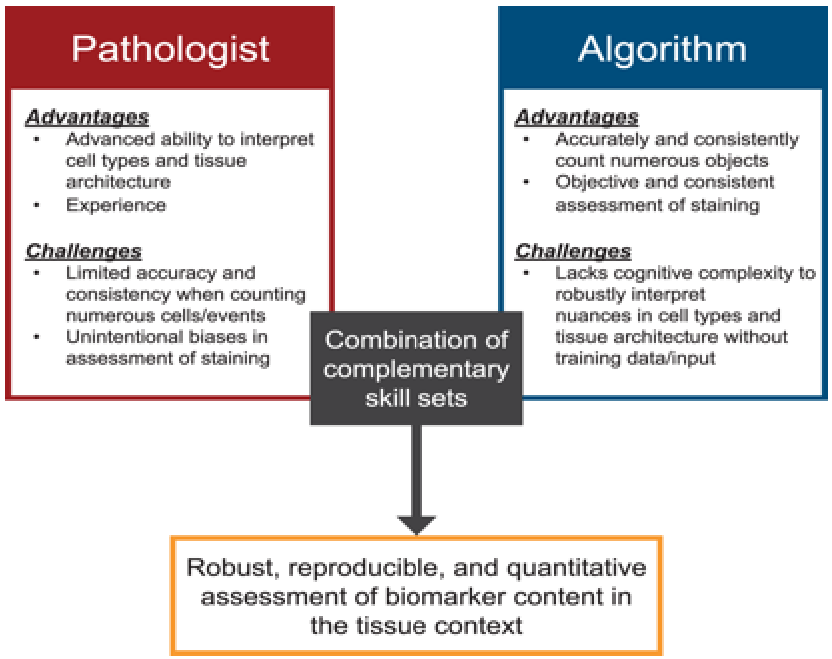
The survey

- Algorithms are needed when workflows are MIA
- Pathologists always needed when etiology is least understood
- Data is always needed

- A: Very High; P: Medium; D: Very High : Prostate
- A: Very High; P: Very High; D: Very High: Sarcoma
- A: Medium; P: Very High; D: Very High: Tall Cell Variant of Thyroid Cancer
- A: Very High; P: Medium; D: High: Breast Cancer

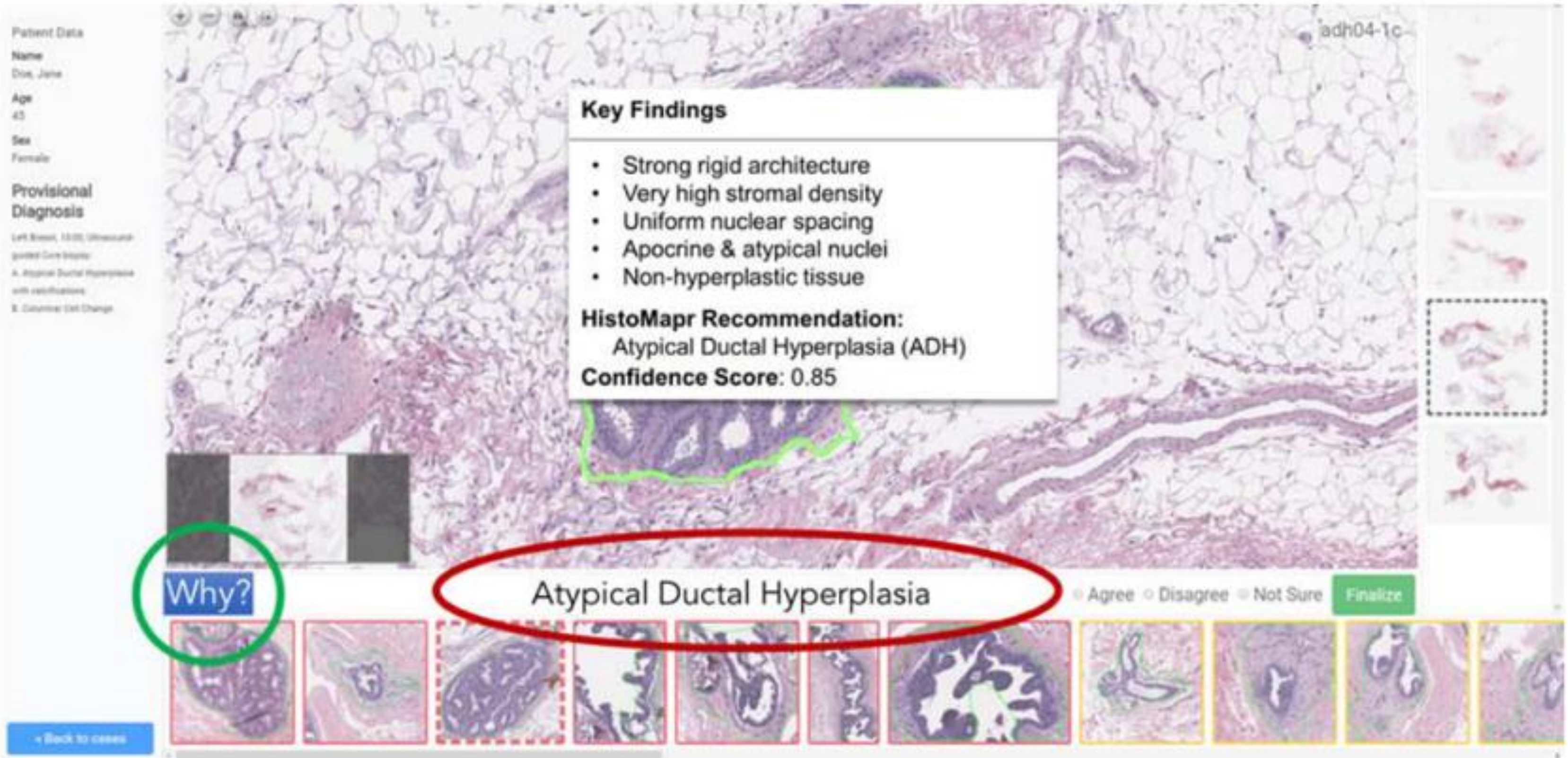
Attaining Gold Standard





From: The Gold Standard Paradox in Digital Image Analysis: Manual Versus Automated Scoring as Ground Truth

Arch Pathol Lab Med. 2017;141(9):1267-1275. doi:10.5858/arpa.2016-0386-RA



HistoMapr-Breast explainable artificial intelligence interface with a "Why?" button. Left panel shows patient information and provisional diagnosis and the right panel has thumbnail images of the patient slides. Regions of interest (ROIs) are automatically detected and presented in the bottom panel. ROIs are triaged based on diagnostic significance from left to right. In this example, HistoMapr analyzed the slide and recommended the diagnosis of atypical ductal hyperplasia for ROI in question, which is a challenging call. Pathologist can hit the "Why?" button to let HistoMapr display Key Findings that led to this recommendation. Please see this image in color online.

doi: 10.1097/PAP.0000000000000264

Thank You for Listening!