Challenges and Rewards of AI Software Applications in Pathology

BEATRICE KNUDSEN, M.D. – PH.D.

MEDICAL DIRECTOR OF DIGITAL AND COMPUTATIONAL PATHOLOGY

ARUP NATIONAL REFERENCE LABORATORIES

Park City, Feb. 9th 2022

Nothing to disclose related to this presentation

The case management cockpit

- Access to all data associated with diagnosis workup
- Clinical workup data sources:
  - Pathology slides and report
  - Laboratory test data
  - Radiology report and images
  - Electronic medical record system
- Pathology imaging data sources
  - Gross room images, light microscopy, fluorescent microscopy, electron microscopy
  - Laboratory medicine images: gel electrophoresis, bacterial/viral cultures, Ova & Parasites, etc.

CAP

2013

Validating Whole Slide Imaging for Diagnostic Purposes in Pathology

Pantanowitz et al; Arch Pathol Lab Med : 137, p1710

- Validation should demonstrate that the WSI system under review produces acceptable digital slides for diagnostic interpretation.
- The intention of validating WSI systems is to permit the clinical use of this technology in a manner that does not compromise patient care.

Brunelli *et al. Diagnostic Pathology* 2014, **9**(Suppl 1):S12
http://www.diagnosticpathology.org/content/9/S1/S12

DIAGNOSTIC PATHOLOGY

2014

PROCEEDINGS Open Access

iPathology cockpit diagnostic station: validation according to College of American Pathologists Pathology and Laboratory Quality Center recommendation at the Hospital Trust and University of Verona

Matteo Brunelli[1*], Serena Beccari[1], Romano Colombari[2], Stefano Gobbo[1], Luca Giobelli[3], Andrea Pellegrini[3], Marco Chilosi[1], Maria Lunardi[2], Guido Martignoni[1], Aldo Scarpa[1,4], Albino Eccher[1]

From 12th European Congress on Digital Pathology
Paris, France. 18-21 June 2014

DIGITAL PATHOLOGY DPA ASSOCIATION

2019

The ACADEMY for Radiology & Biomedical Imaging Research

Models for implementing artificial intelligence in pathology practice

Douglas Hartman, U of Pittsburg

https://slidetodoc.com/models-for-implementing-artificial-intelligence-in-pathology-practice/

- Standardized measurements and techniques
- Standardized image formats and interchange
- Reference studies and datasets

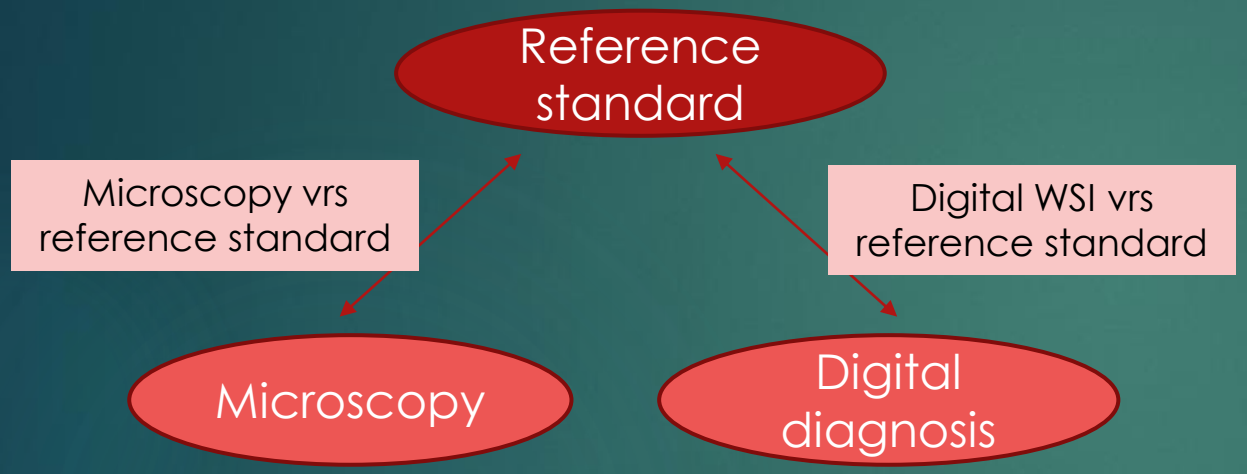
Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology

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

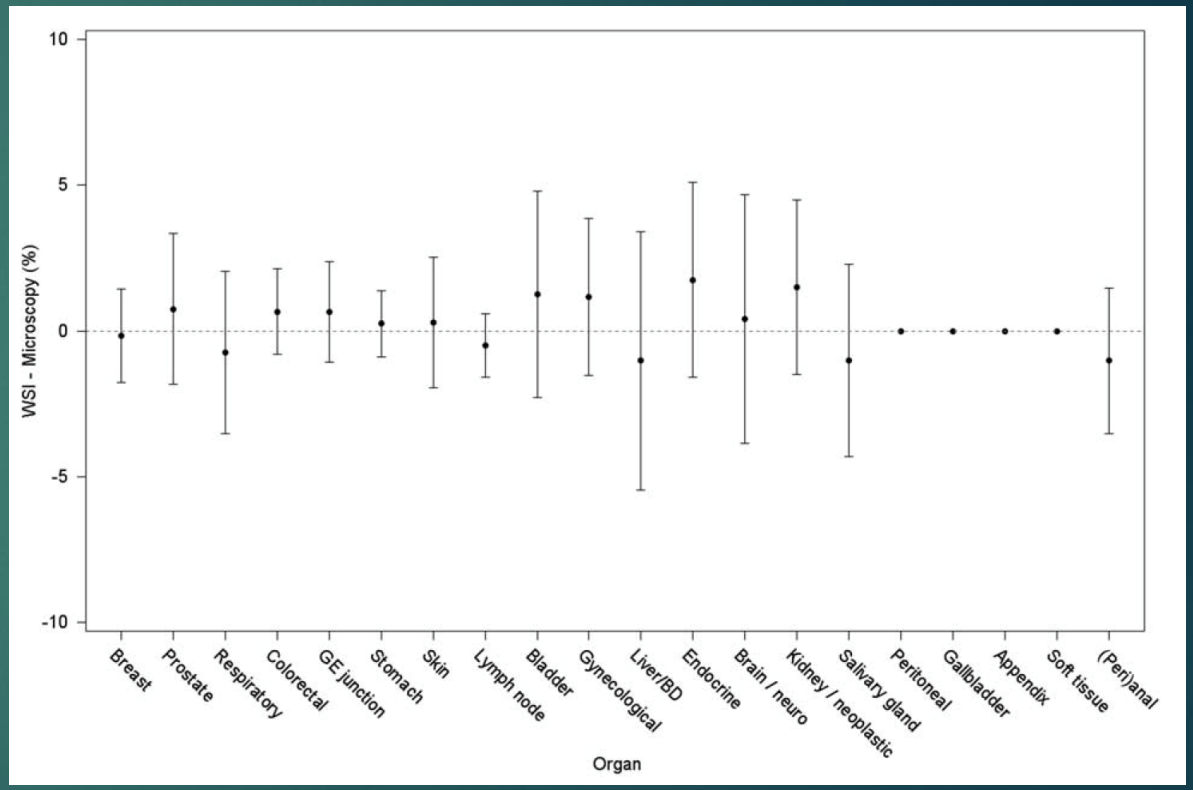
Am J Surg Pathol • Volume 42, Number 1, January 2018

(Mukhopadhyay et al. (Clive Taylor USC)

Non-inferiority study design



4 centers
8 enrolment pathologists verify primary diagnosis used as reference standard
16 reading pathologists (M (20 cases) → washout (4w) →digital WSI
3 pathologists to judge concordance



https://documents.cap.org/documents/wsi-teaching-presentation.pdf

What should be done to validate a whole slide digital imaging system for diagnostic purposes before it is placed in clinical service ?

- Pathologist must validate slide set of at least 60 H&E cases (FFPE, frozen, hemepath)
- & 20 IHC and special stain cases
- Concordance glass/digital $\geq$ 95% (2 week washout)
- Good practice standards from 2013 : each lab should do their own validation which must include a pathologist, emulate a real world situation and encompass the entire WSI workflow

Events forming digital pathology

2000 — Electronic medical record system

2015 — Radiology PACS system

2020 — Commercial digital pathology slide management systems

2017 — Philips primary diagnosis

2020 — Leica primary diagnosis

2020 — Paige primary diagnosis

2022 — Paige A.I. algorism

Vendor agnostic viewer cleared by NYS for primary diagnosis

Journal of the American Medical Informatics Association, 28(9), 2021, 1874–1884
doi: 10.1093/jamia/ocab085
Advance Access Publication Date: 14 July 2021
Research and Applications

Research and Applications

Integrated digital pathology at scale: A solution for clinical diagnostics and cancer research at a large academic medical center

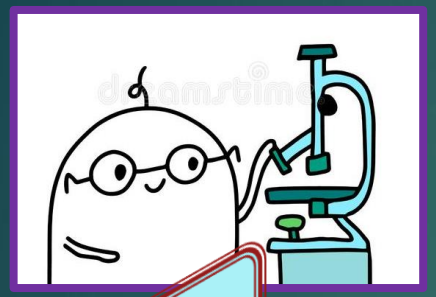
Peter J. Schüffler[1,2], Luke Geneslaw[1], D. Vijay K. Yarlagadda[1], Matthew G. Hanna[1], Jennifer Samboy[1], Evangelos Stamelos[1], Chad Vanderbilt[1], John Philip[1,3], Marc-Henri Jean[1], Lorraine Corsale[1], Allyne Manzo[1], Neeraj H. G. Paramasivam[4], John S. Ziegler[1], Jianjiong Gao[5], Juan C. Perin[4], Young Suk Kim[6], Umeshkumar K. Bhanot[1], Michael H. A. Roehrl[1,7], Orly Ardon[1], Sarah Chiang[1], Dilip D. Giri[1], Carlie S. Sigel[1], Lee K. Tan[1], Melissa Murray[1], Christina Virgo[1], Christine England[1], Yukako Yagi[1], S. Joseph Sirintrapun[1], David Klimstra[1], Meera Hameed[1], Victor E. Reuter[1], and Thomas J. Fuchs[1,8]

[1]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [2]Institute of Pathology, Technical University of Munich, Munich, Germany, [3]Department of Health Informatics, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [4]Department of Information Systems, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [5]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [6]School of Medicine, Stanford University, Stanford, California, USA, [7]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, New York, USA, and [8]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Corresponding Author: Prof. Dr. Peter J. Schüffler, Department of Pathology Technical University of Munich; peter.schueffler@tum.de

- Data on digital pathology implementation at a large tertiary care medical center
- Digital slide viewer installed at 4 hospital systems and used over 3yrs by 926 pathologists and researchers evaluating 288 903 digital slides.
- Integrated digital pathology solution for sign-out, research and education
- Different functionalities are required for the three end user groups
- Solution to assure data and patient privacy is most critical factor
- The framework includes A.I. software for diagnosis of prostate cancer, basal cell carcinoma & breast cancer metastasis

Digital pathology infrastructure



A.I. software plug-ins for primary diagnosis and IHC quantification

Digital slide viewer

Slide management system

Server for whole slide images

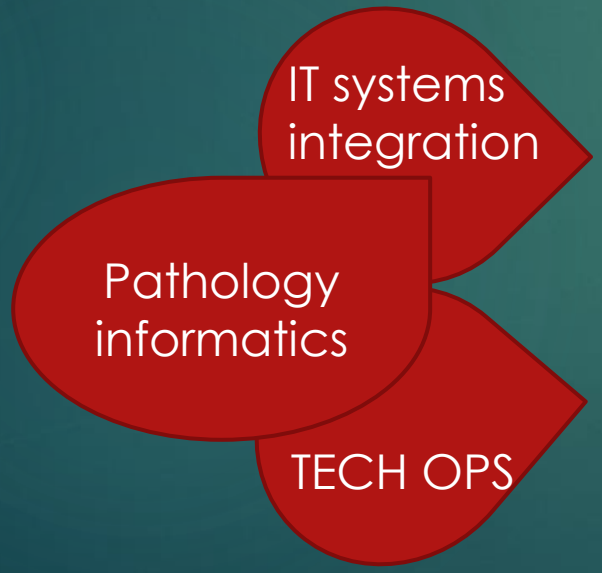
Digital slides

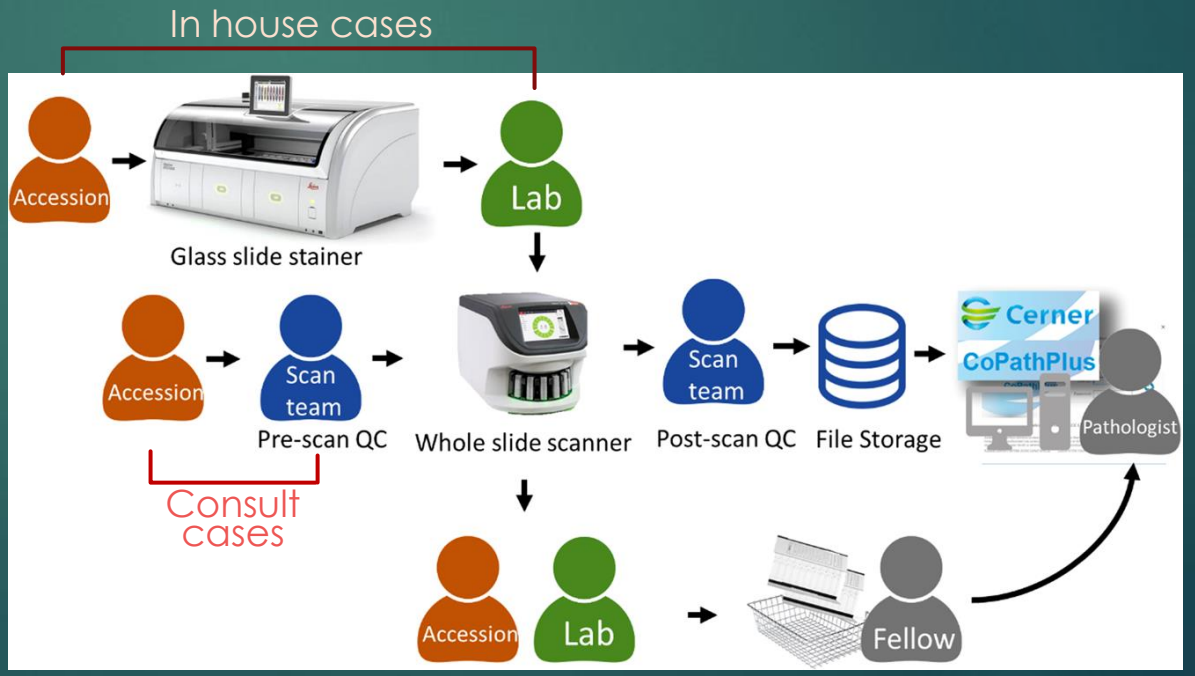
Slide scanner

Clinical implementation of digital pathology requires a team

CHALLENGES for DIGITAL pathology

- Integration of the digital pathology computer and software systems with other laboratory information systems in pathology





Clinical implementation of digital pathology requires a team

CHALLENGES for COMPUTATIONAL pathology

- To bring research grade algorithms into clinical practice

Why should pathologists adopt digital pathology ?

- Efficiency
- Accuracy
- Structured, accessible information and slide organization
- Job satisfaction of pathologists and lab personnel
- Client satisfaction
- Improved communication
- Research opportunities
- Education

Resistance to digital sign out in pathology

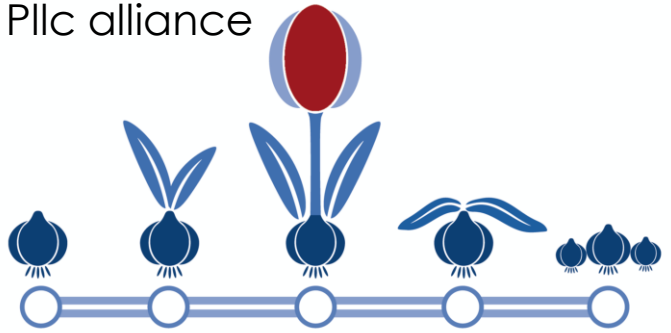
- Distrust of algorithm and computer assistance
- Less control over sign out process
- Less interactions with colleagues
- Speed
- Ergonomics
- Joy of microscopy
- Change in workflow

How to overcome resistance and move to a digital sign out

- Partnership between pathologists
- Discovering value in DP
- Educational materials
- Partnership with slide management systems vendor
- Customized interfaces
- High-quality DP products (requires evaluation)
- Internet speed and ergonomics

DIGITAL PATHOLOGY DPA ASSOCIATION

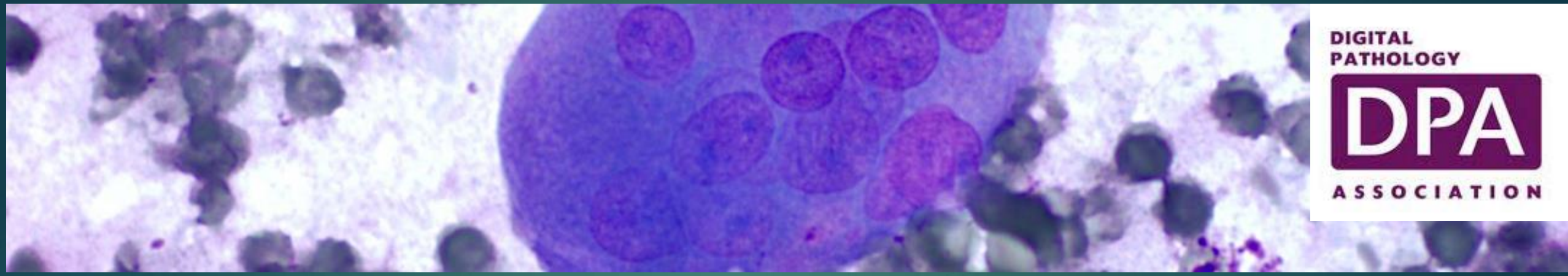
Pllc alliance



What do I need to sign out cases at home

1. March 2020, CMS temporarily waived the requirement for remote locations to have separate CLIA licenses. Advocacy by CAP committees to convert temporary to permanent regulation.
2. The validation study using 60 H&E cases and 20 IHC cases with glass and digital reads. > 95% concordance for diagnostic components affecting patient management
3. Remote readiness:
   - Computer/workstation with large monitor and fast network bandwidth
   - Remote desktop connection through institutional virtual private network with 2-factor authentication

Digital Pathology and education



DIGITAL PATHOLOGY DPA ASSOCIATION

Digital Anatomic Pathology Academy

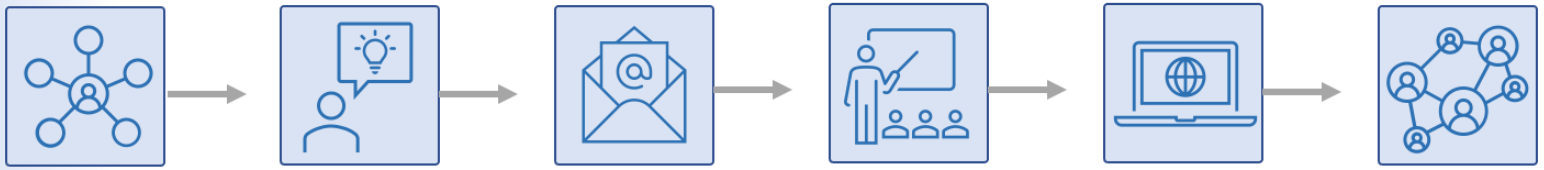
Cloud-based platform which provides annotated digital slides with diagnosis and relevant information of morphology and ancillary testing

Digital pathology and regulatory science

A regulatory science initiative to harmonize and standardize digital **pathol ogy** process es to speed up innovation to patients.

Pathology Innovation Collaborative Community

The Alliance for Digital Pathology and AI/ML



You value Collaborations

You have a Regulatory Science Project

You propose your project to PIcc

You present to steering committee

PIcc helps organize the project

PIcc is a network to find interested collaborators

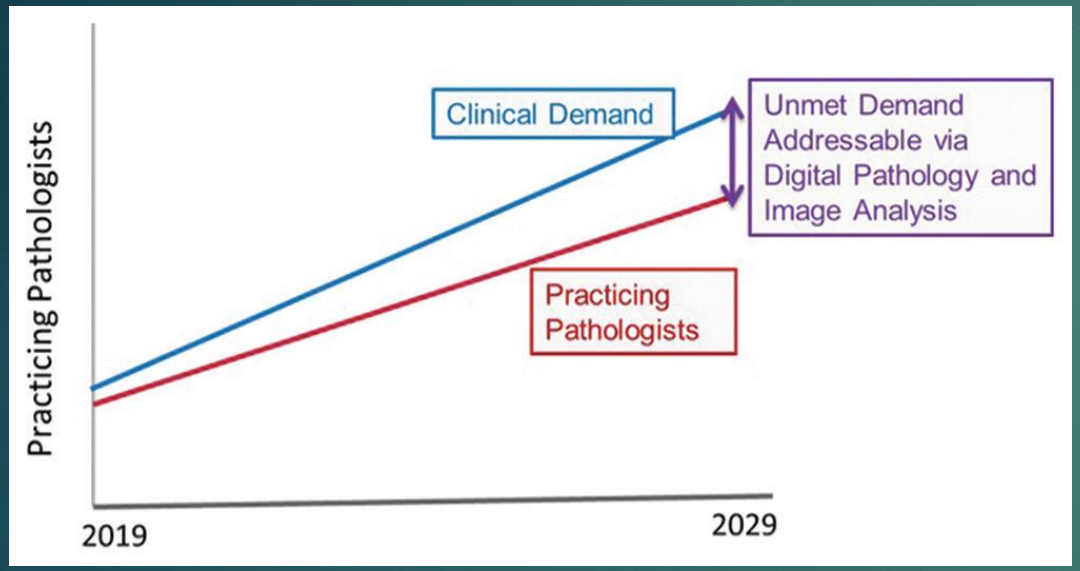
Focus is NOT on competitive product development

PIcc does NOT actively participate in your project All interested members are

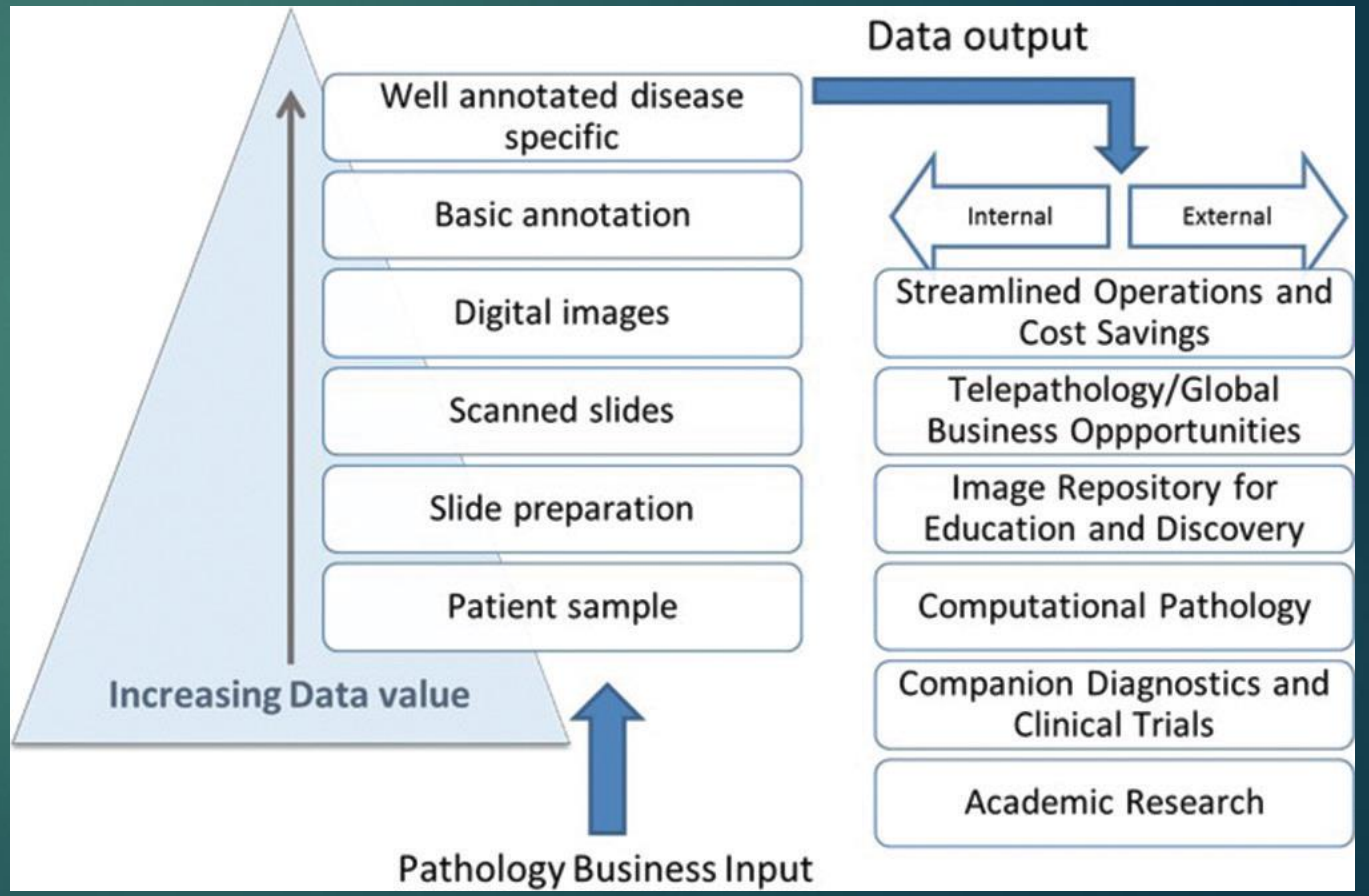
PIcc is a collaborative community that provides the infrastructure to connect stakeholders

Value proposition of digital pathology

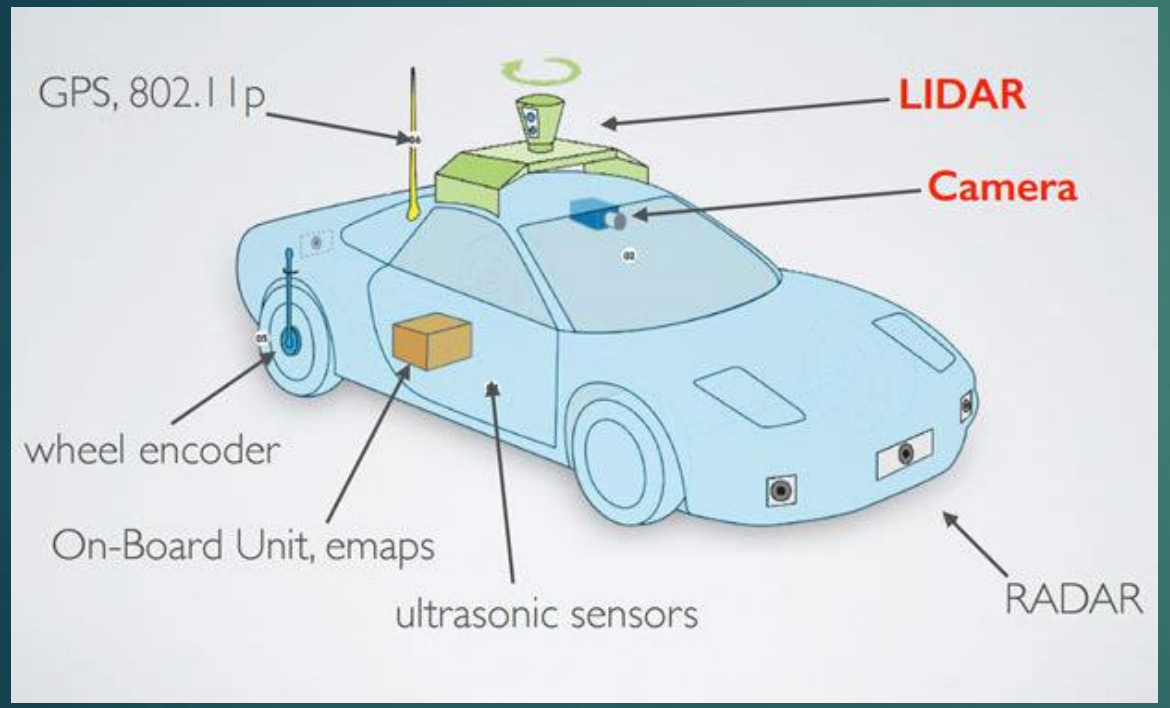
Shortage of pathologists



Value for computational pathology



What is computational pathology ?



Mechanics

Data Processor

Electronics

DIGITAL PATHOLOGY

engine — Slide management system (SMS)

wheels — Slide scanners

COMPUTATIONAL PATHOLOGY

Data input — Digital slides

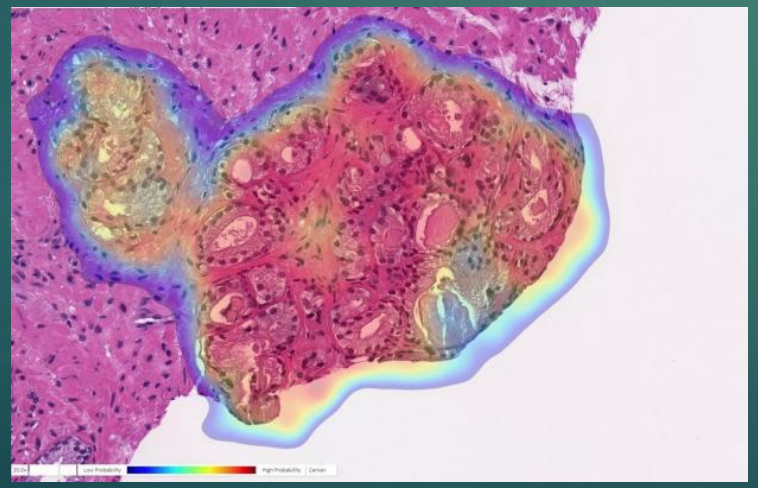
Data output — Algorithms

FDA approves algorithm for prostate cancer diagnosis

Paige

September 21st, 2021

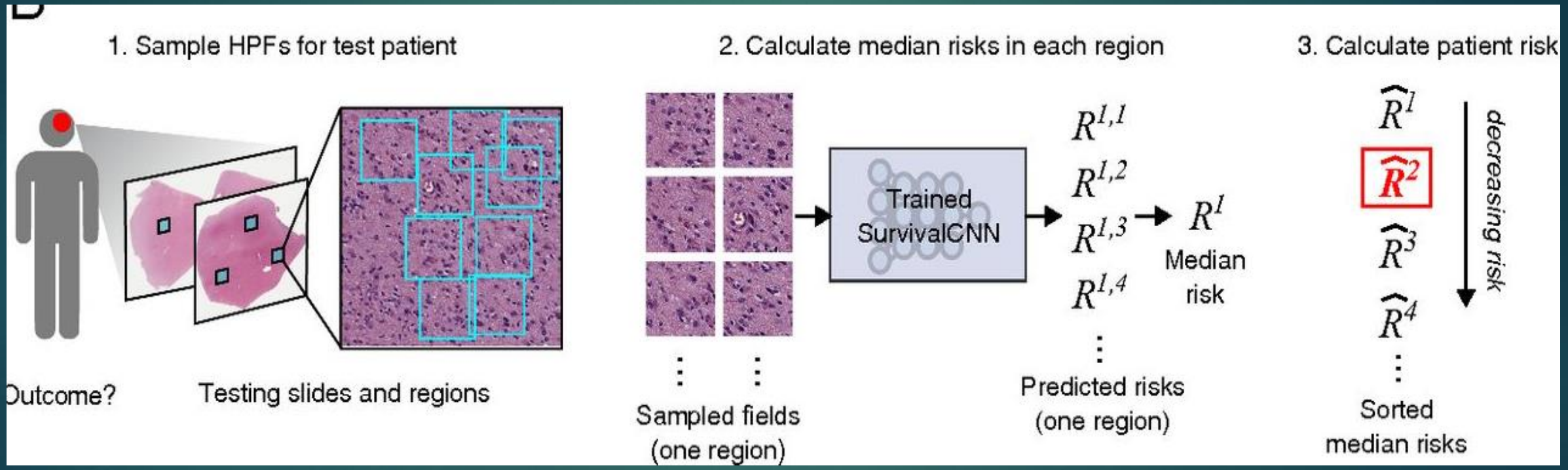
- Algorithm can be used as second opinion for cancer detection
- approval based on a study where 6 pathologists examined 527 digitally scanned prostate biopsy slides. The pathologist made two assessments, one with and one without the program's help.
- The software improved detection of cancer on individual slide images by 7.3% on average compared to unassisted reads.



IBEX

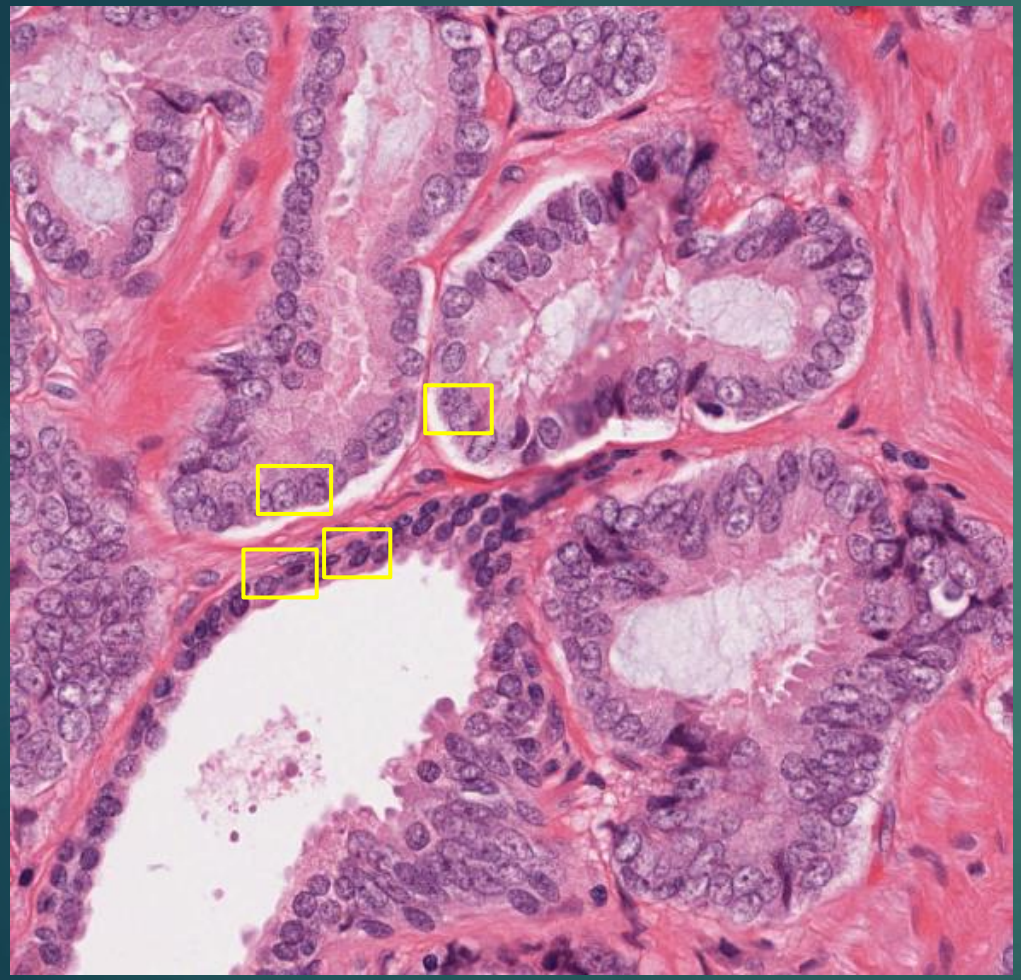
How do machine learning algorithms work ?

Level 1 : counting positive cells in IHC stained slides
Level 2 : cancer diagnosis and outline of cancer regions
Level 3 : prognosis and treatment recommendation



Predicting cancer outcomes from histology and genomics using convolutional networks.
Mobadersany & Lee Cooper PNAS, 2018

Pathologist-inspired algorithm development



1. Criteria established by pathologist do diagnose prostate cancer:
- Loss of basal cell layer
- Nuclear enlargement
- Nucleolus
- Luminal border

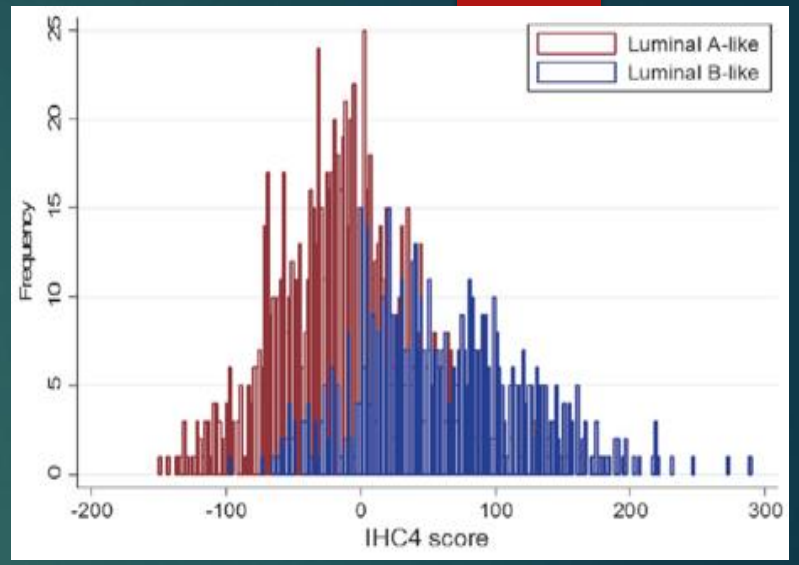
2. Force algorithm to learn features of these criteria

3. Visualize features that the algorithm learned

4. This specific approach does not work for grading, which is based on gland architecture

IHC quantification

- FDA approved algorisms since 2007
- Algorithm linked to slide scanner
- Home – grown systems
- Semi-automated, pathologists marks region to quantify
- Ki-67, breast panel, PD-L1



Modern Pathology (2019) 32:1244–1256
https://doi.org/10.1038/s41379-019-0270-4

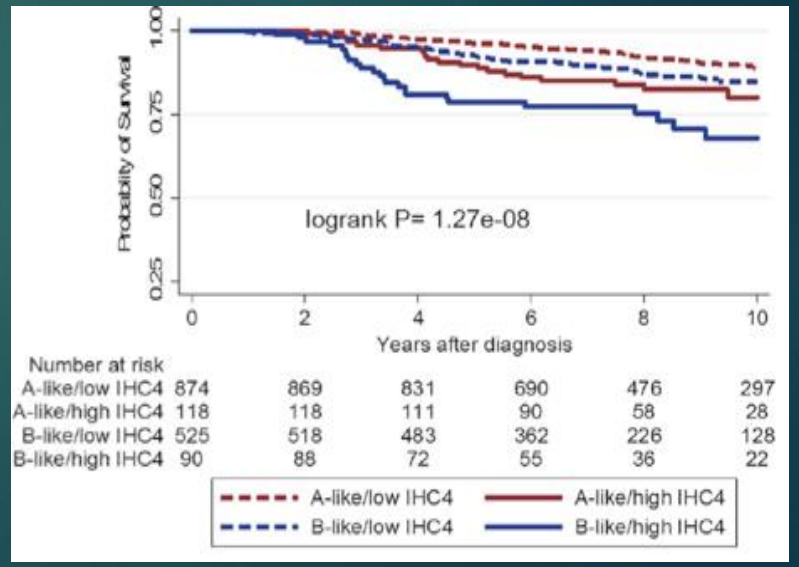
USCAP

ARTICLE

Check for updates

Combined quantitative measures of ER, PR, HER2, and KI67 provide more prognostic information than categorical combinations in luminal breast cancer

Mustapha Abubakar[1,2] · Jonine Figueroa[3] · H. Raza Ali[4] · Fiona Blows[5] · Jolanta Lissowska[6] · Carlos Caldas[4,7,8] · Douglas F. Easton[5,9] · Mark E. Sherman[10] · Montserrat Garcia-Closas[1] · Mitch Dowsett[11,12] · Paul D. Pharoah[4,9]

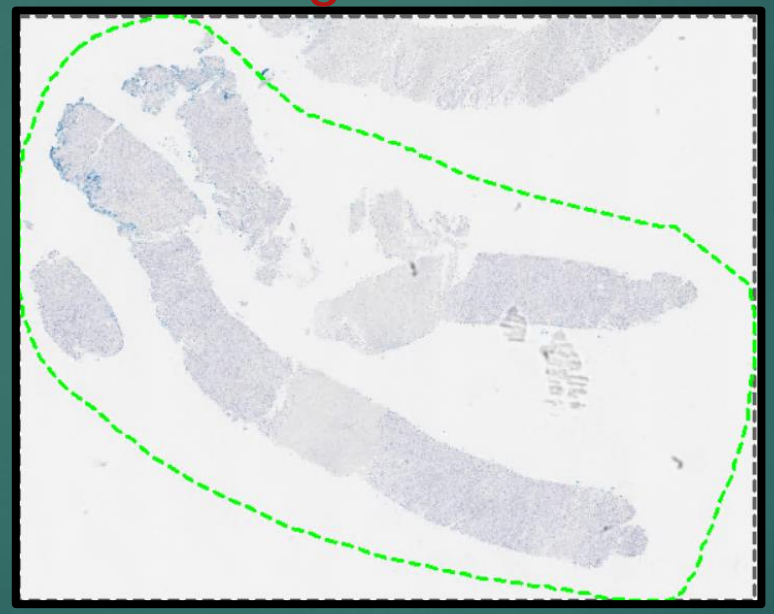


Automated PD-L1 scoring workflow

Step 1- The computer learns to overlap images from different slides

H&E

PD-L1 negative control

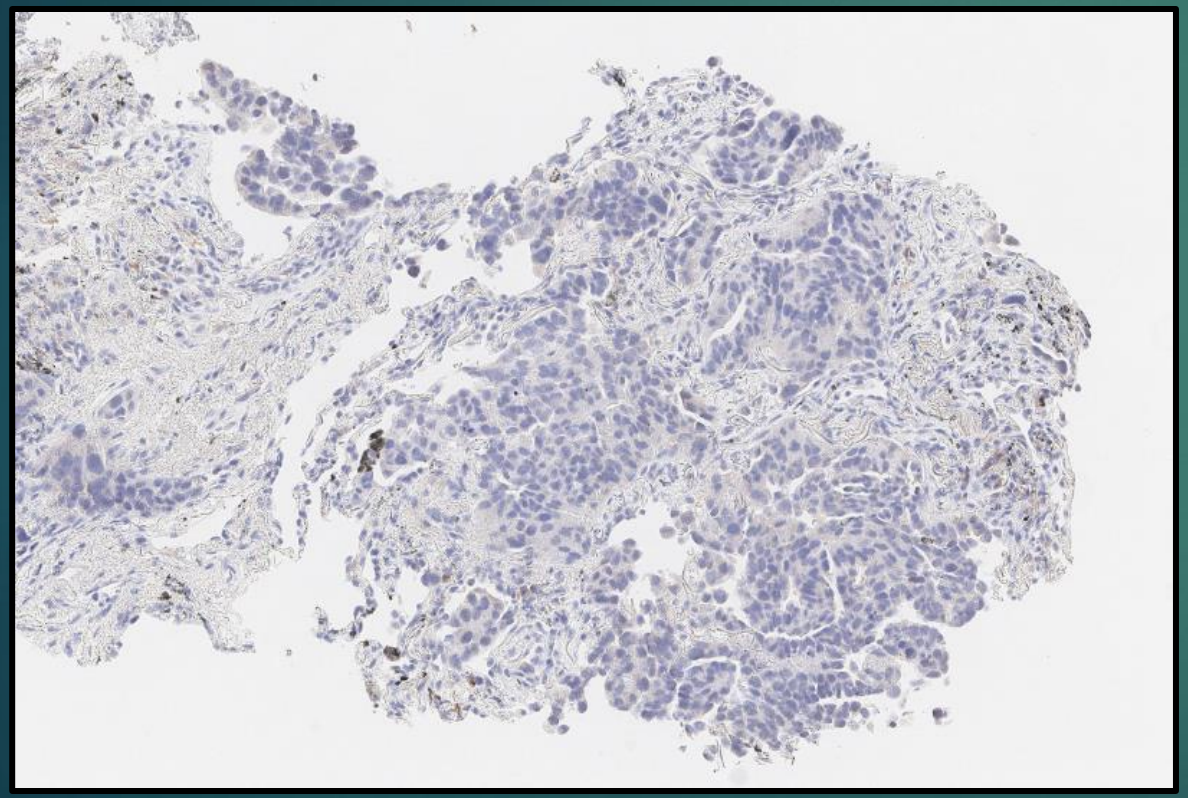


PD-L1

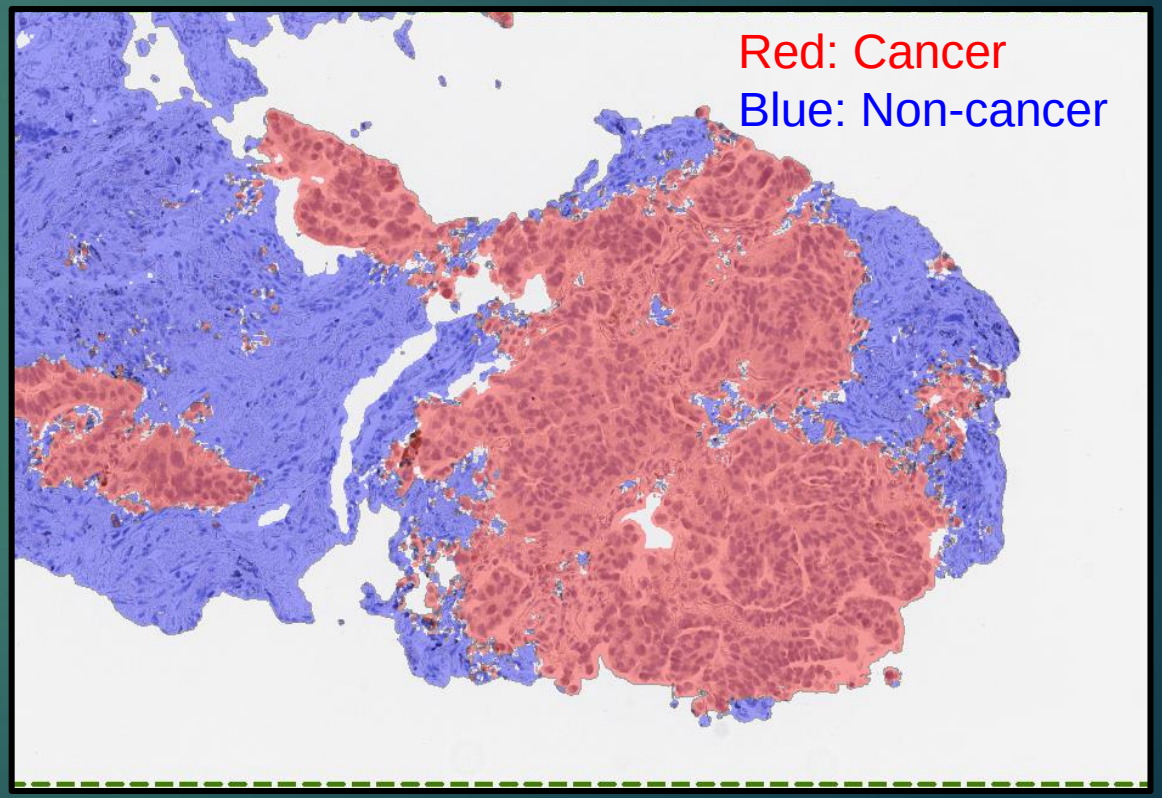
Step 2: outline areas of necrosis

Step 3 - Computer learns to outline cancer regions

Original image

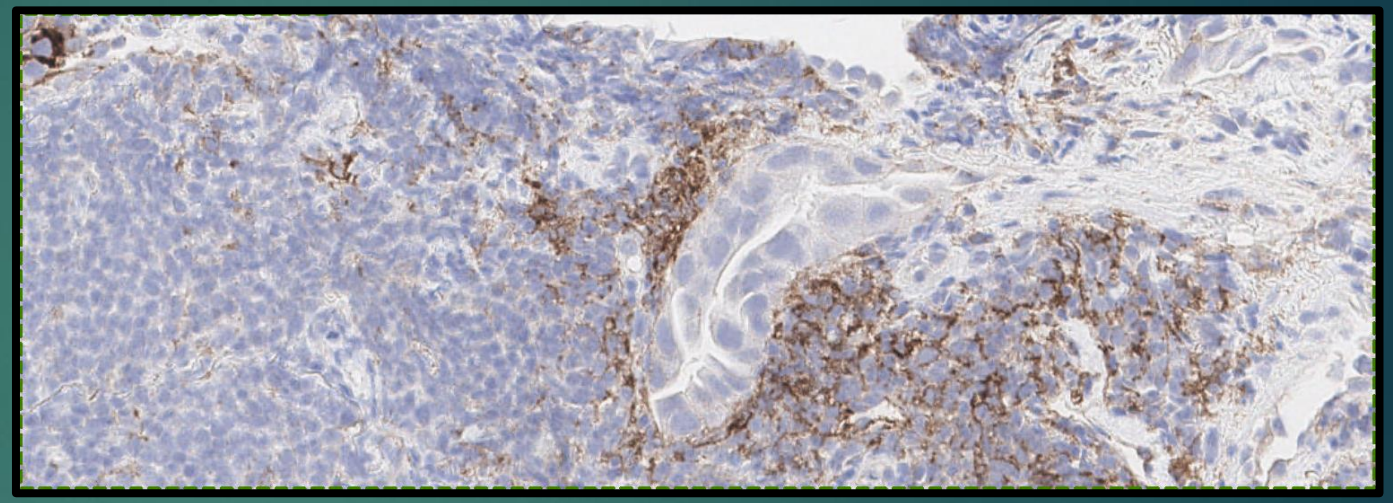


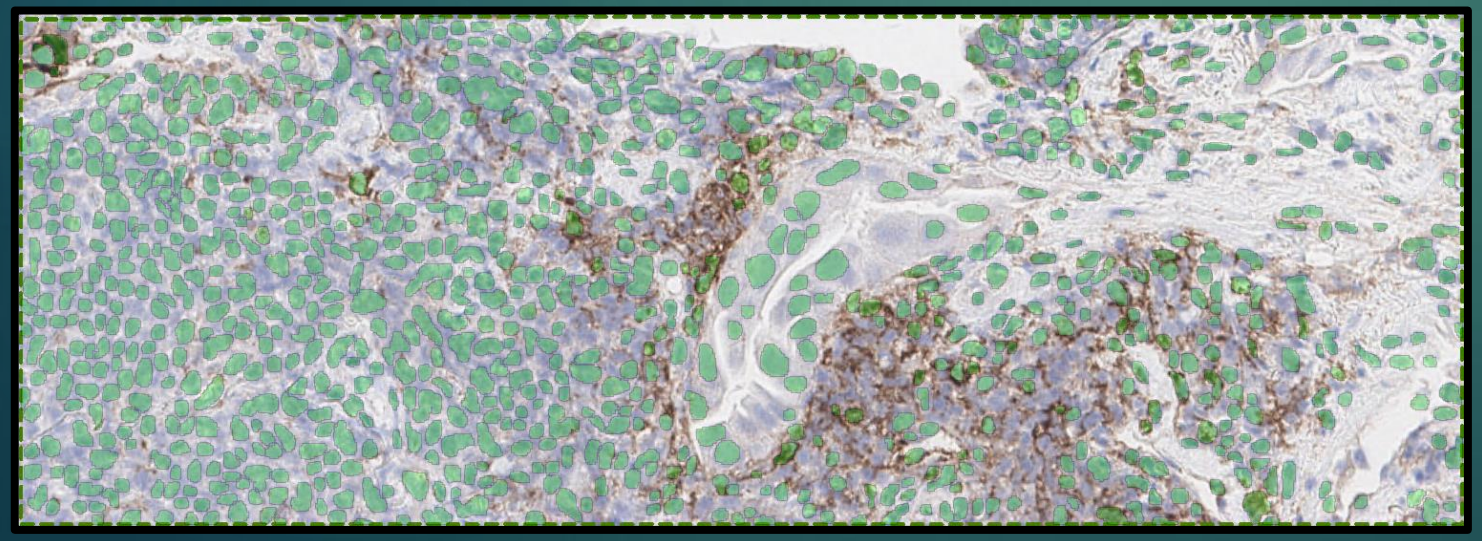
Computer generated cancer map



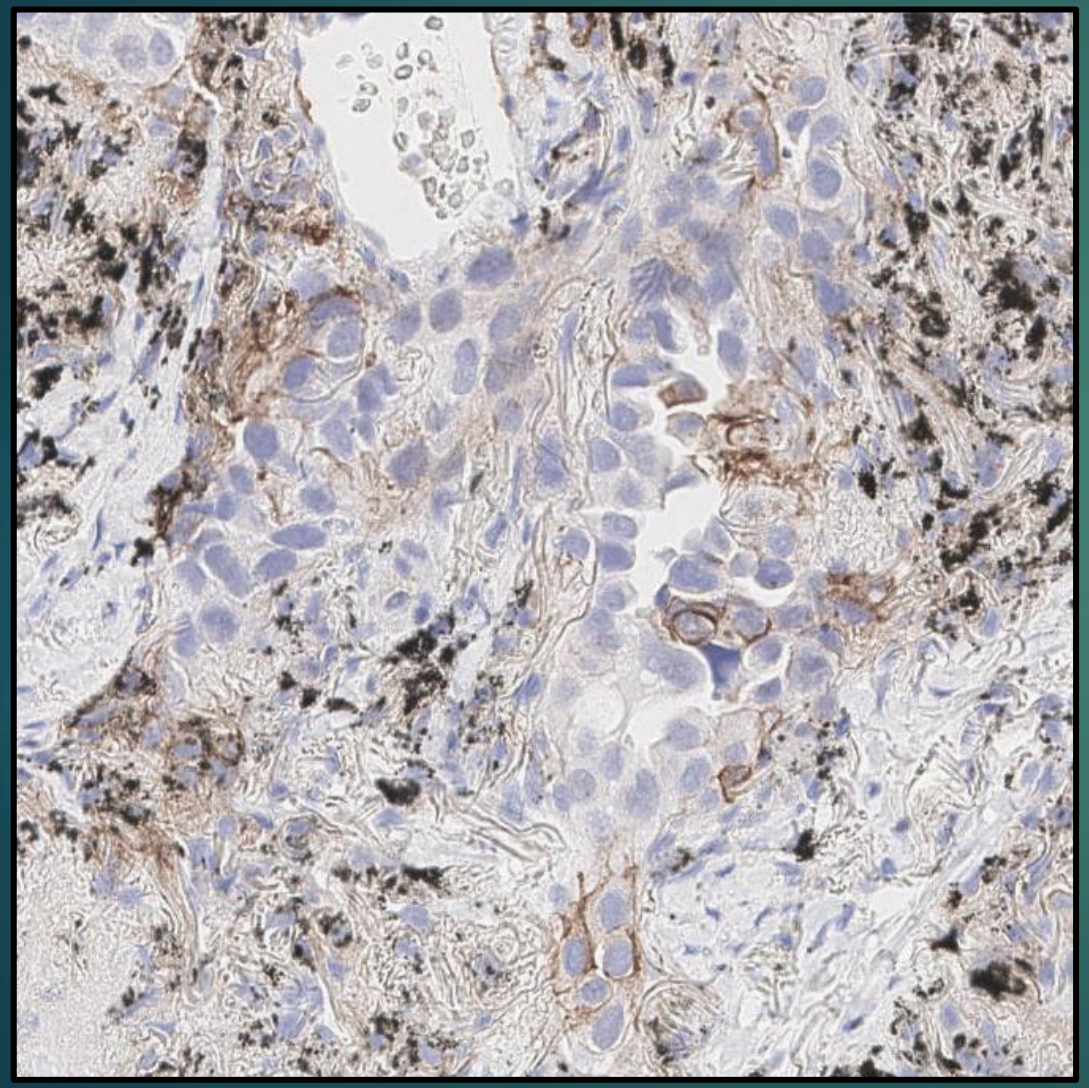
Examples of computer-generated annotations in IHC slides – step 4

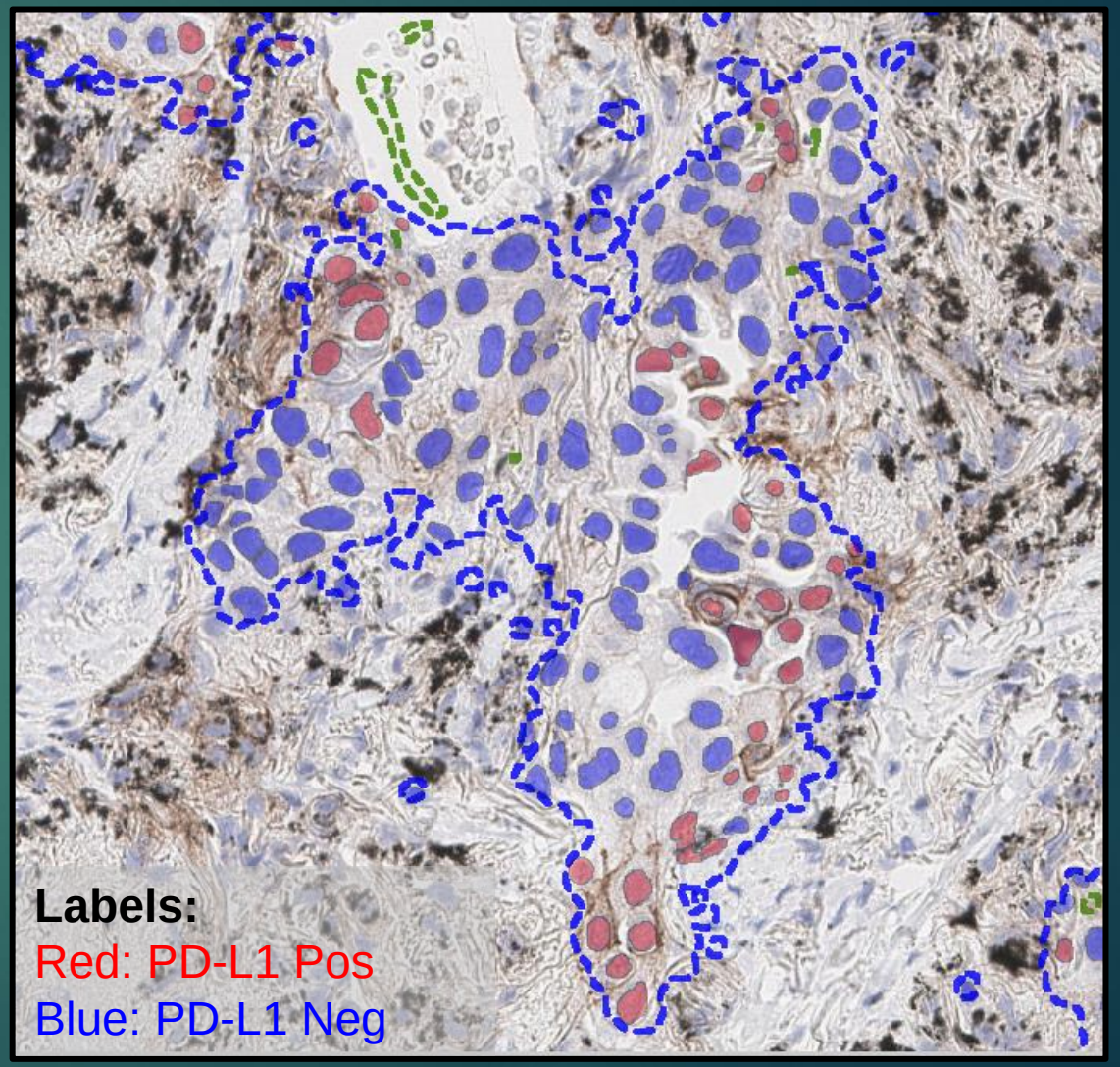
Nuclear outlines and immune cell infiltration





Quantification of PD-L1 positive cells – step 5





Performance evaluation of the algorithm is critical at your practice location

- Don't trust vendors (yet)
- Algorithms are challenging to optimize
- Off the shelf commercial algorithm need to be tested at your practice location for its performance
- Performance has to be evaluated for each step in the algorithm if there is a problem with the algorithm
- Be involved in testing to understand what the algorithm does
- Data migration into pathology reports

Future opportunities in digital and computational pathology

- Automation of anatomic pathology
- Increased efficiency
- Increased accuracy (reimbursement for using algorithm)
- Fast second opinion
- Quantitative data from slides
- Prognostic and treatment related information
- May be able to replace certain expensive genomic testing

Future challenges in digital and computational pathology

- Expensive infrastructure
- Integration into existing IT structure
- New operational workflows
- Acceptance by pathologists
- Regulatory framework
- Pricing and cost efficiency

Thank you for your attention

QUESTIONS ?