DISSERTATION REPORT

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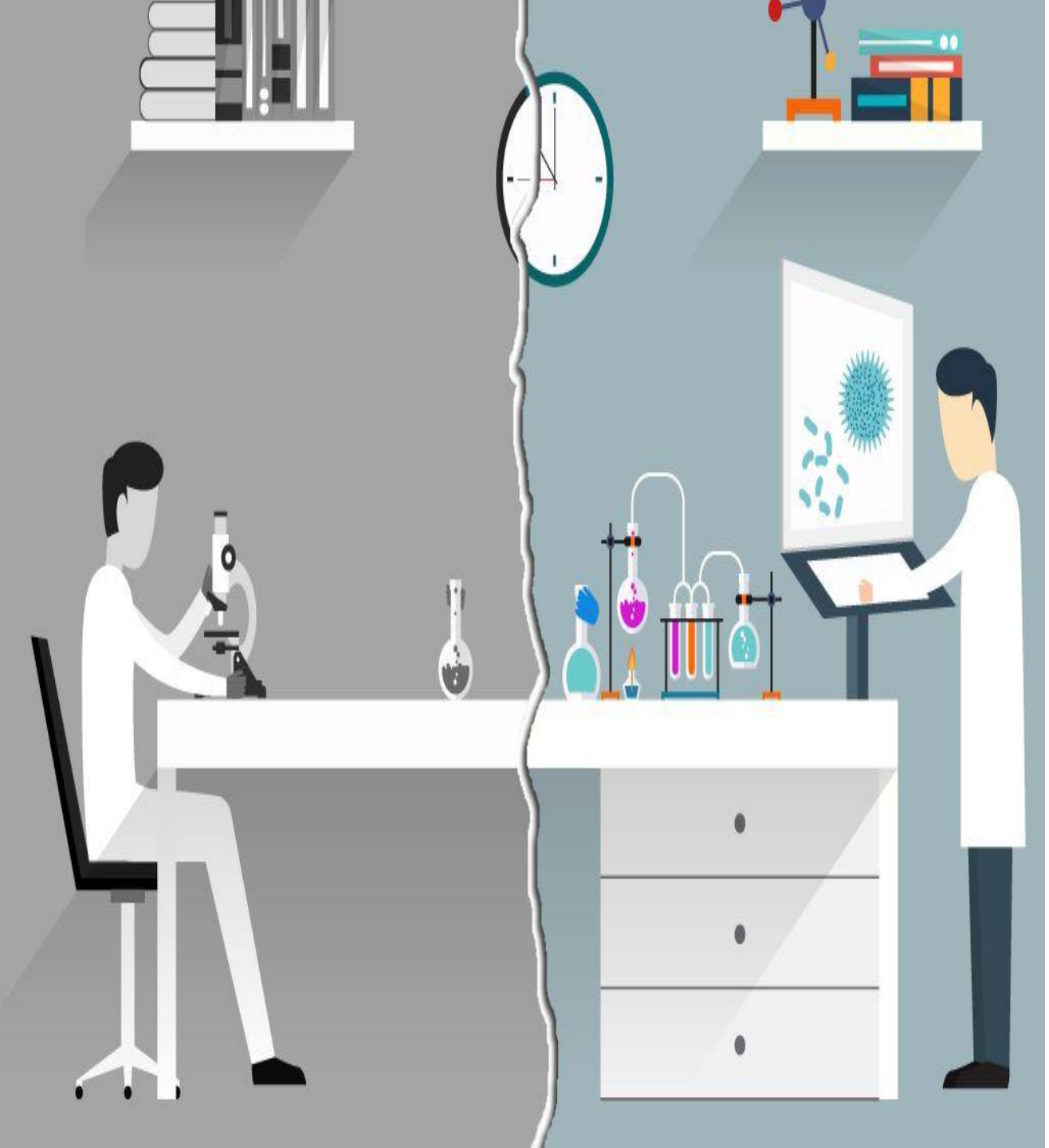


DIGITAL PATHOLOGY

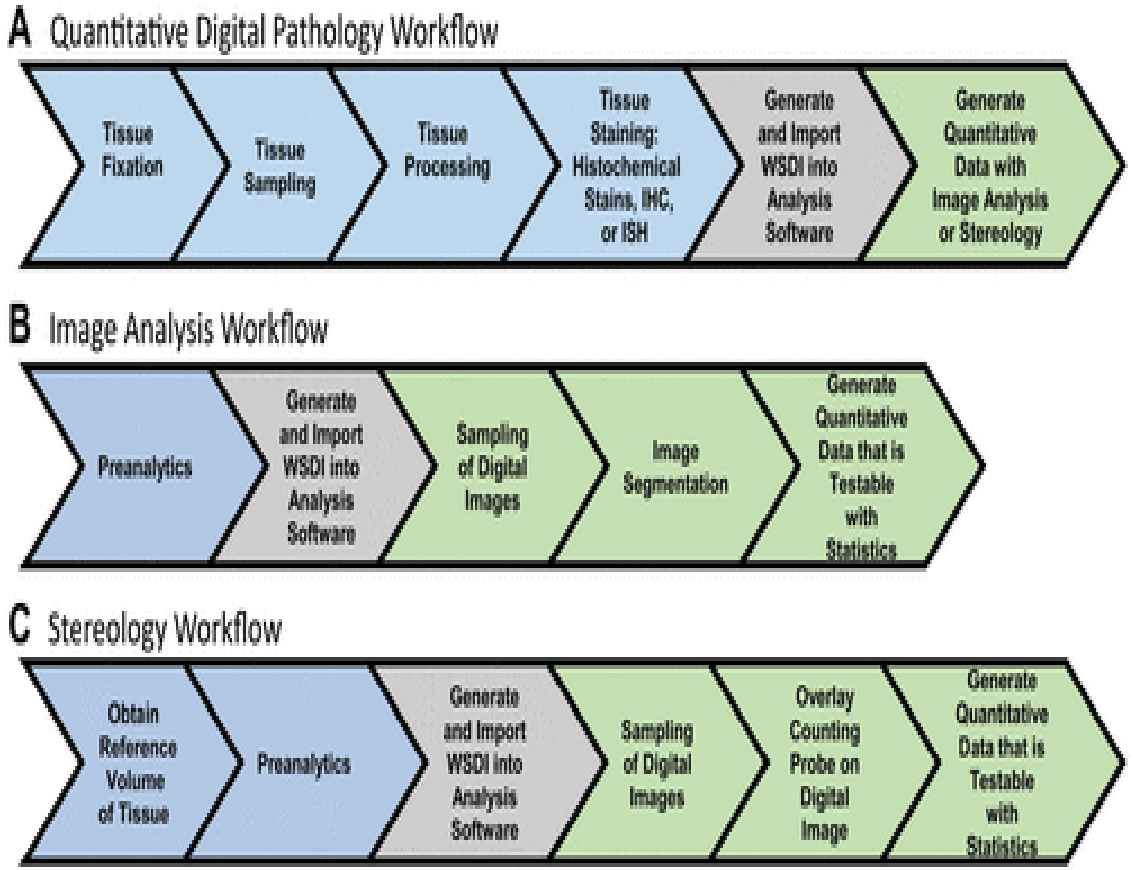
ADVANTAGES, LIMITATIONS, EMERGING PERSPECTIVES & VALUE IN IMMUNO-ONCOLOGY RESEARCH & DEVELOPMENT

INTRODUCTION

- The advent of digitized images to pathology has propelled this traditional field into what is now described as digital pathology (DP).
- Digital images and video streams can be shared in real-time.
- Digital images lend themselves to computational pathology (CPATH), both for basic measuring and counting and for advanced machine learning (ML) tasks.

Quantitative Digital Pathology

- The development of whole slide images means that digital slides can be viewed, managed, and shared from the Cloud and analyzed on a computer monitor.



Stereology vs Image Analysis

	Stereology	Image Analysis
ADVANTAGES	• Gold standard for quantitative analysis of tissues • Minimal to no assumptions • Provides precise and unbiased measurements • Able to accurately measure volumes, number of cells, surface area, etc.	• Easily automated • Quantitative results are obtained more rapidly than with stereology, so more amenable to high throughput • Excellent when used for IHC, ISH, and special stains when contrast allows easy segmentation of an image
LIMITATIONS	• Considerable amount of time is required to perform stereology • Typically requires the investigator to obtain an initial reference volume and monitor changes to the volume during tissue processing to account for shrinkage	• Less rigorous and assumptions are required in many instances, which introduces bias • This technique provides measurements of relative change (%), which is typically a ratio of the ROI to the total tissue or other denominator • Counts 2D profiles, which overestimates the number of objects counted • Less precise than stereology

OBJECTIVES

1. To study about digital pathology implementations.
2. To study about combining technology, artificial intelligence, and occupational wellbeing challenges, as well as potential variations in the pathologist’s career, research future possibilities.
3. To study about how quantitative digital pathology can add value to immune-oncology research and development.

METHODOLOGY

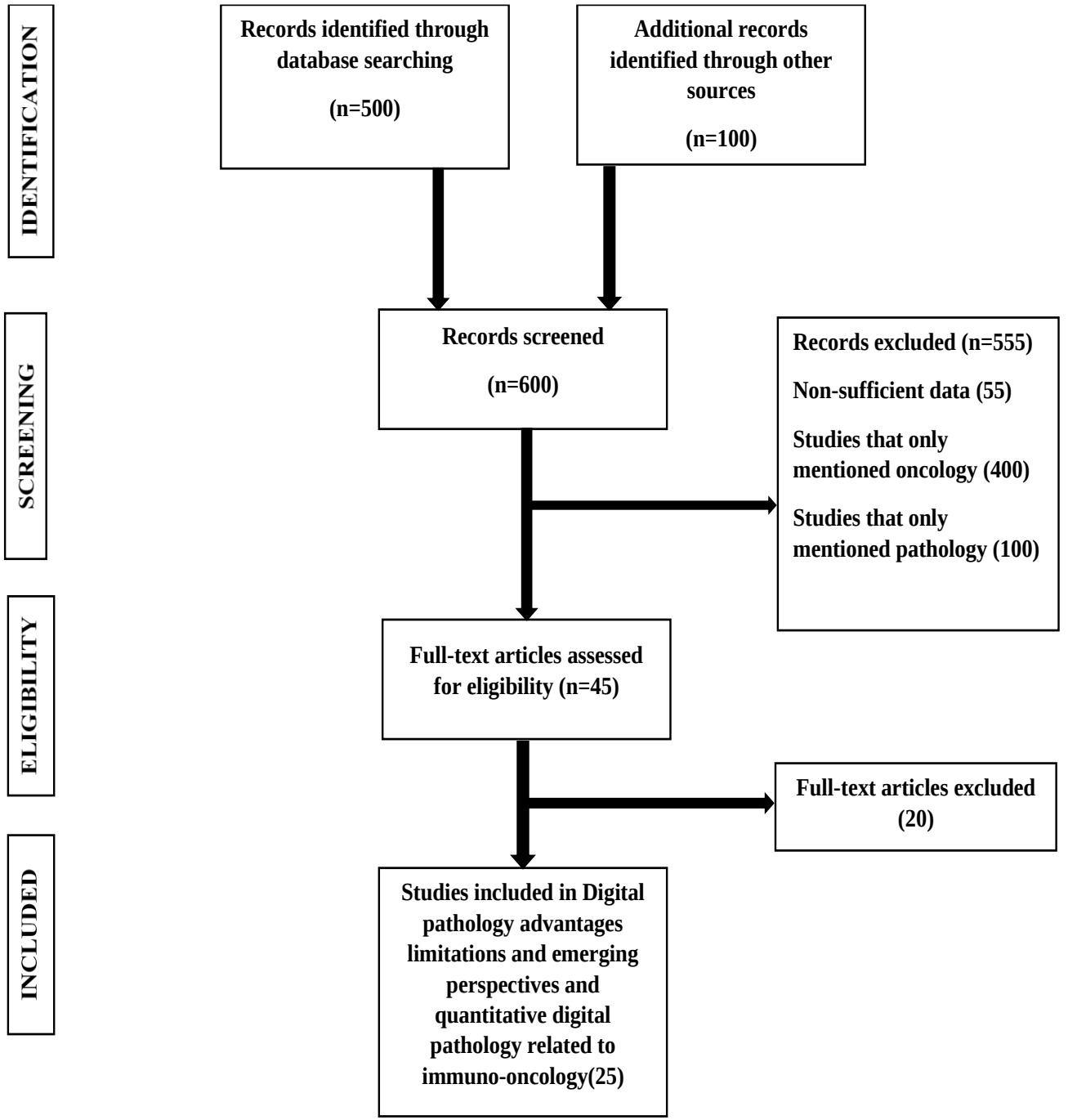
Research Design- Systematic Review

Literature Review- 25 articles were selected out of 45 articles from various databases like Medline, Google Scholar, ProQuest, JSTOR and Science Direct.

Secondary Data - The study is based on the secondary data available from various agencies and in the cancer care.

Inclusion Criteria	Exclusion Criteria
Full text articles	Abstracts
Original research, Meta-analysis, Systematic review, Scoping review	Newspaper articles, conference presentations, blogs
English language articles	Other language articles
Digital pathology articles related to immuno-oncology	Articles related to only oncology
	Questionnaire studies

METHODOLOGY



REVIEW OF LITERATURE

STUDY	AUTHORS	FINDINGS
Introduction to digital image analysis in whole-slide imaging	Famke Aeffner, Mark D Zarella, Nathan Buchbinder, Marilyn M Bui, Matthew R Goodman, Douglas J Hartman, Giovanni M Lujan, Mariam A Molani8, Anil V Parwani, Kate Lillard, Oliver C Turner, Venkata N P Vemuri, Ana G Yuil-Valdes, Douglas Bowman-2019	This study aims to review the basics of tissue image analysis and supply pathologists with basic data concerning the capabilities, applications, and customary workflows of those new tools. during this review, they tend to define the fundamental classes of obtainable software package solutions, potential analysis methods, technical concerns, and general algorithmic readings.
Computational pathology definitions, best practices, and recommendations for regulatory guidance	Esther Abels, Liron Pantanowitz, Famke Aeffner, Mark D Zarella, Jeroen van der Laak, Marilyn M Bui, Venkata NP Vemuri, Anil V Parwani, Jeff Gibbs, Emmanuel Agosto-Arroyo, Andrew H Beck, Cleopatra Kozlowski- 2019	This review provides a historical perspective and describes the potential clinical profit and high harm to enlisting in analysis and applications during this field. Best practices for implementing process pathology workflows square measure conferred.
A Practical Guide to Whole Slide Imaging	Mark D. Zarella, PhD; Douglas Bowman; Famke Aeffner, DVM, PhD; Navid Farahani, MD; Albert Xthona; Syeda Fatima Absar, MD; Anil Parwani, MD, PhD; Marilyn Bui, MD, PhD; Douglas J. Hartman, MD- 2018	The implementation of the WSI may be a many-sided and inherently knowledge base effort that needs contributions from diagnostician technicians and management. associate understanding of the present challenges for implementation and therefore the strengths and success of the technology can facilitate future users notice the simplest path to success.
Quantitative Image Analysis for Tissue Biomarker Use	Lara, Haydee MS, PhD; Li, Zaibo MD, PhD; Abels, Esther MS; Aeffner, Famke DVM, PhD; Bui, Marilyn M. MD, PhD; ElGabry, Ehab A. MD; Kozlowski, Cleopatra PhD; Montalto, Michael C. PhD; Parwani, Anil V. MD, PhD, MBA; Zarella, Mark D. PhD; Bowman, Douglas BSE; Rimm, David MD, PhD; Pantanowitz, Liron MD, MHA- 2018	Tissue biomarkers have accrued their utility in research, malady identification and prediction of therapeutic response. In qualitative assessments, there was a stable modification in providing additional quantitative assessments for these biomarkers. Therefore, the applying of quantitative image analysis has become an essential tool for biomarker examination of deep tissues in such a context.
Dissecting the business case for adoption and implementation of digital pathology	Giovanni Lujan, Jennifer C Quigley, Douglas Hartman, Anil Parwani, Brian Roehmholdt, Bryan Van Meter, Orly Ardon, Matthew G Hanna, Dan Kelly, Chelsea Sowards, Michael Montalto, Marilyn Bui, Mark D Zarella, Victoria LaRosa, Gerard Slootweg, Juan Antonio Retamero, Mark C Lloyd, James Madory, Doug Bowman- 2021	The focus of this written report is to teach pathologists, labs, and alternative stakeholders on the business and monetary concerns concerned in reworking digital pathology workflows.
Bringing Open Data to Whole Slide Imaging	Sébastien BessonRoger LeighMelissa LinkertChris AllanJean-Marie BurelMark CarrollDavid GaultRiad GozimSimon LiDominik LindnerJosh MooreWill MoorePetr WalczyskoFrances WongJason R. Swedlow- 2019	Faced with the necessity to support additional and additional WSI file set-ups, their team has lengthy the long-lived community file format (OMETIFF) for usage. This set-up utilizes the most specifications of dustup to hoard multiple resolution (or "pyramid") depictions on a sole slide in an exceedingly svelte and economical approach.

STUDY	AUTHORS	FINDINGS
PanNuke: An Open Pan-Cancer Histology Dataset for Nuclei Instance Segmentation and Classification	Jevgenij GamperEmail Navid Alemi KoohbananiKsenija BenetAli KhuramNasir Rajpoot- 2019	It so demonstrates that the learned data is proficiently resettled to form new knowledge sets. These three streams square measure either genuine on all prevailing public standards or genuine by skillful pathologists, and finally coalesced and genuine to get a hefty complete division and examination dataset PanNuke.
Active Learning for Patch-Based Digital Pathology Using Convolutional Neural Networks to Reduce Annotation Costs	Jacob CarseEmail Stephen McKenna- 2019	Convolutional neural networks were competent on patches that are little, every comprising one nucleus. The K-center sampling strategy showed diffident will increase.
Virtualization of Tissue Staining in Digital Pathology Using an Unsupervised Deep Learning Approach	Amal LahianiEmail Jacob GildenblatIrina KlamanShadi AlbarqouniNassir NavabEldad Klaiman- 2019	Several target-specific stains, at the side of IHC, area unit needed to spotlight precise assemblies within the tissue. a picture of the stained tissue could also be just about generated because of the shortage of tissue and therefore the tedious staining procedure.
Evaluation of Color Pre-processing on Patch-Based Classification of H&E-Stained Images	Francesco BianconiEmail Jakob N. KatherConstantino C. Reyes-Aldasoro- 2018	Quantitatively compare the color and texture descriptor combined effects of. they need found that color pretreatment, in most cases, adversely affects accuracy. particularly once used with color descriptors.
Automated Segmentation of DCIS in Whole Slide Images	Nikhil SethEmail Shazia AkbarSharon Nofech-MozesSherine SalamaAnne L. Martel- 2019	Here they need trained many UNet styles (a deep neural convolutional network planned to yield risk maps) to section the whole DCIS of the slide image and confirm the perfect patch field of deem required to achieve sensible accurateness at the slide level.
Deep Features for Tissue-Fold Detection in Histopathology Images	Morteza BabaieHamid R. Tizhoosh- 2019	They compared 5 pre-trained convolutional neural networks (CNNs) of various depths in useful extraction to characterize tissue wrinkles. They additionally enraptured a typical sorter to tell apart tissue collapsible with hematoxylin and eosin-stained diagnostic assay samples from a standard tissue.
Histopathological Image Analysis on Mouse Testes for Automated Staging of Mouse Seminiferous Tubule	Jun XuHaoda LuHaixin LiXiangxue WangAnant MadabhushiYujun Xu- 2019	The WSI of the mouse gonad read contains many regular customs. On the opposite hand, every regular customs workplace additionally includes numerous forms of germ cells from different microscopic anatomy areas. These factors create it tough to divide clear germ cells and regions within the cross section of the mouse gonad.

RESULTS AND DISCUSSION

TELEPATHOLOGY TO WSI

- Technical advances in scanning speed and decreased costs have made whole slide imaging (WSI) the standard for future, large-scale, high-throughput DP.

- WSI enables tissue work-up, cutting, and staining at the local pathology department, followed by immediate scanning of slides, which can be later accessed by the reporting pathologists. Pathologists can subsequently view data either on-site or remotely.

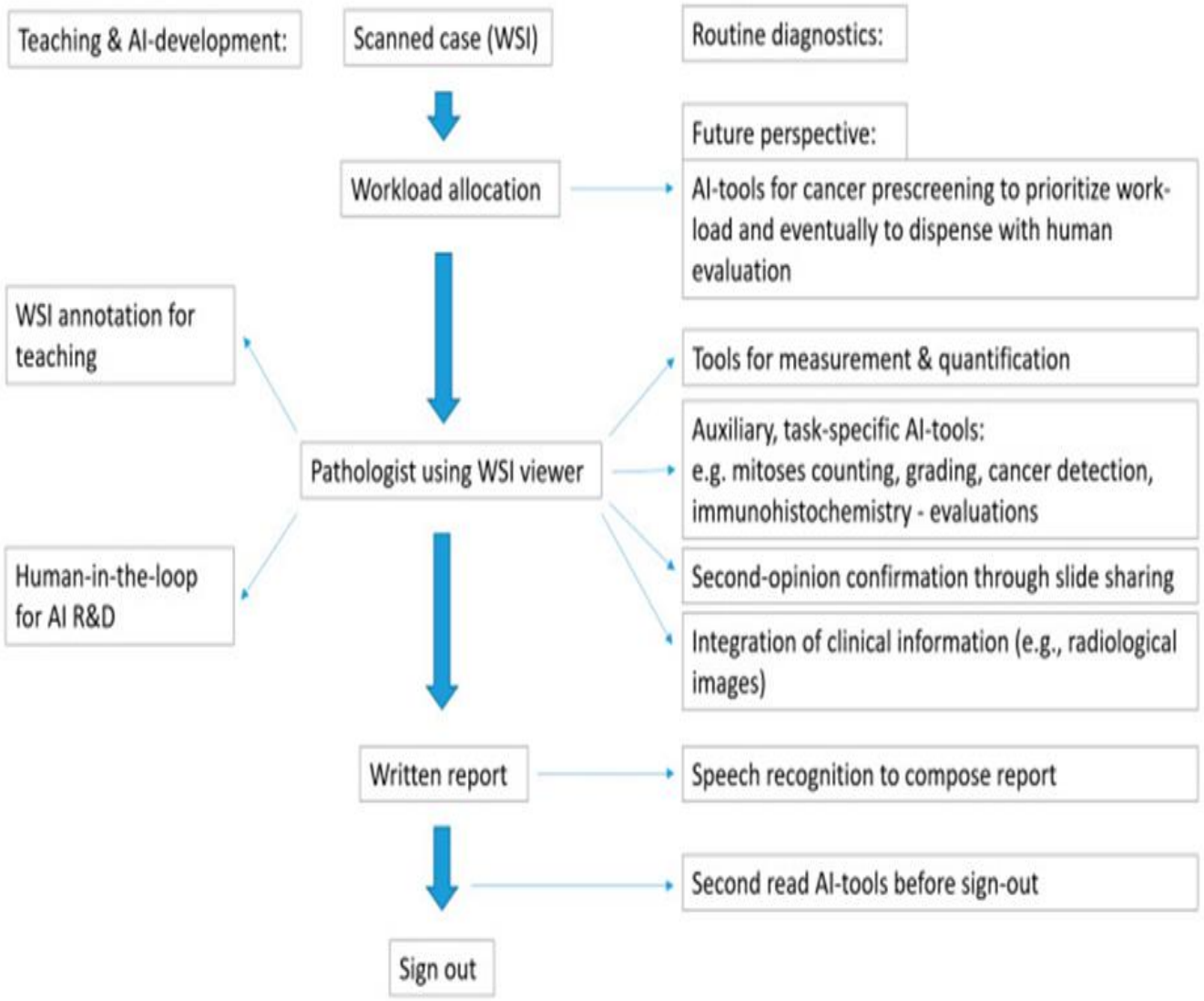
Concordance of Digital Pathology with Glass Slides

- In the aforementioned non-inferiority study used for FDA market authorization, an equal discordance rate between glass slides (4.6%) and WSI (4.9%) slides was seen when each slide type was reevaluated ≥4 weeks after initial diagnosis.
- Major WSI vs. glass discordance rate was not significant at 0.4% (95% confidence interval (CI) (−0.3–1.01)).
- In a review of discordant cases, no consistent inaccuracies due to WSI were observed. Other studies have found concordance rates to range from above 90% to over 95%.

Critical Quality Parameters in WSI for Diagnostic Imaging

- If the manufacturer has not performed external validation, in-house validation should be performed on a sufficient number of representative cases.
- The time between digital and glass slide comparison should be at least two weeks to guarantee unbiased evaluation (“washout period”) by the same person.
- Accurate color rendition is essential and necessitates WSI scanners’ regular calibration against a standardized reference (established: “IT8.7/1 target”, 28 greys/264 colors).
- DP data can be stored in open or proprietary formats.
- The state of the art technical implementation of WSI in routine diagnostics is complex, requires expertise, human resources, and a continuous focus on technical advances.

The Integrated DP Work-Flow



Experience from DP Implementations in Routine Diagnostics Using WSI

- The Eastern Quebec Telepathology Network (EQTN) is one of the most extensive real-life applications for DP. The network provided remote intra-operative consultation and histopathological second opinion.
- In 2017, one report was published with five-year DP implementation experience on 6700 cases/35,500 slides and reported a >90% digitally only sign out rate.
- The DP use at the Memorial Sloan Kettering Cancer Center, US, including a DP experience survey for pathologists' feedback; 48% of respondents would not have felt comfortable with DP sign-out without glass slides available, and 15% felt uncomfortable even with glass slides available.

Computational Pathology (CPATH)

- It spans a wide range of applications that comprise in order of ascending complexity image-enhancing features, measuring and quantification, graphical highlighting/pre-selection by heat mapping, and lastly, fully automated assessments.

- CAPTH has also successfully been applied for research purposes to link digital images to clinical data directly.

Cost-Effectiveness Considerations

- If DP use is limited as for biomarker evaluation/quantification or second read tasks, total costs will increase as DP costs are incurred in addition to glass slide evaluation.
- At the Memorial Sloan Kettering Cancer Center's pathology department in the US. This academic center produced >125,000 slides a month as of 2017. The transition from research to routine WSI was initiated in 2015 and implemented on a subset of cases.
- Cost-efficiency analyses to date are few, often estimated and derived from academic single-center experiences that cannot easily be generalized.

Digital Pathology and Occupational Health—Computer Vision Syndrome

- Between 64% and 90% of computer users experience visual symptoms such as dry eyes, headaches, eyestrain, burning eyes, diplopia, and blurred vision when using (computer) screens.
- Musculoskeletal injury from computer use has been estimated to account for at least half of work-related injuries in the US.
- Experiences from a Dutch DP routine implementation reported on 23 pathologists, of whom 65% regarded DP to be “ergonomic” or “very ergonomic” but close to 10% experienced DP as only “slightly ergonomic”.
- A 10% rate of DP users discontent with DP ergonomics was also reported, but complaints might be higher in close to full-time DP reporting, as only a third of pathologists opted to sign out more than half of their cases digitally.

Digital Pathology and the Pathologist's Profession

- A 2016 study by McKinsey assessed the current automation potential across US professions and found the lowest potential with professions "managing others" at 9% of work-time, together with those applying expertise at 18%, the latter applicable to pathologists.
- Will AI make the pathologist's workday less taxing? In conjunction with AI, DP may assist with tasks strenuous for human assessment.
- DP will create a global market for histopathology services, where language barriers, first of all, delineate competing labor-markets. Salaries for pathologists might come under pressure in high-income markets due to increased competition with lower-wage countries.

Important Open Challenges and How They Could Be Addressed

- **Regarding the problem of non-transparent AI algorithms-** Explainable AI, which is a subfield of AI, is dedicated to exposing complex AI models to humans in a systematic and interpretable manner and one of the ways to allow for human scrutiny and ultimately the building of trust in this technique.
- **Occupational health-** Evaluations need to systematically address musculoskeletal as well as ocular injury.
- **Cost-effectiveness analyses-** Based on standardized criteria, Results need to be stratified by type of department (academic/non-academic).

Digital Pathology (DP) Feature	Possible Advantages	Possible Disadvantages
In-house telepathology	○ Quick second opinion ○ Social distancing (COVID-19 pandemic)	Second opinion overuse (interrupted work-flows) ○ Decreased interpersonal (face-to-face) communication
Extramural telepathology	○ Service for remote/understaffed areas ○ Specialization through DP in low volume labs ○ Home-office use ○ Healthcare cost reduction through global histopathology market	○ Social isolation in remote telepathology ○ Loss of routine on-site expertise through home office ○ Wage competition through global histopathology market
Consultation telepathology	○ Quick access possible ○ No physical slide transfer ○ Lower threshold for consultation due to shorter turnaround time	○ No tissue block available for additional stains/molecular assays ○ Consulted pathologist unaccustomed to work-up (stains/scanner calibration) at the primary center ○ Compatibility issues due to diverse proprietary DP formats ○ Possible medico-legal implications due to restricted work-up
WSI-general	○ No physical slide distribution ○ No fading of stored slides ○ No irretrievable/lost slides ○ Shorter sign-out time ○ Reduced misidentification of slides due to barcoded slides automatically allocated to the case ○ Easy dynamic workload allocation (e.g., management of backlogged work, redistribution in case of sick leave)	○ Time to evaluable-ready slide increased due to additional scan time ○ Integration into a laboratory information system (LIS) for full efficiency gains needed → possible costs for LIS update ○ Regular calibration required (scanners/displays) ○ Small particles omitted by scan → manual checking for rescan ○ Artifacts (out-of-focus areas, digital stitching artifacts) ○ Increased IT-dependence (IT-downtime) compared to optical microscopy
WSI-reporting/user experience	○ Parallel (side-by-side) viewing, digital slide superposition ○ Shorter sign-out time ○ Quick access to prior slides → less immunohistochemistry ○ Facilitates slide presentation at multidisciplinary tumor board ○ Easy image sharing in clinical communication ○ Computational pathology possible (see below) ○ Occupational health: less neck strain, more flexible posture	○ Slower evaluation compared to optical microscopes ○ Mostly only single focus plane in routine DP → difficulties with interpretation ○ Extra training for safe practice required (perceived insecurity on digital sign-out) if not DP from career start ○ Easy availability of prior digital slides might shift medico-legal onus towards more extensive re-examination → increased workload ○ Dual infrastructure generally necessary (glass and digital) ○ Occupational health: Computer Vision Syndrome (CVS)

Digital Pathology (DP) Feature	Possible Advantages	Possible Disadvantages
WSI-Image Analysis, ML/AI	○ Faster/efficient and more accurate measurements/quantifications ○ Exact quantification of tumor cell content for molecular analyses ○ Digital enhancement of image features ○ AI for second-read safety net ○ Direct link morphology to clinical parameters “novel biomarker” beyond human recognition ○ Inspection/correction of suggestions from AI-apps in development on WSI-viewer: “human-in-the-loop” interaction	Benefit of more accurate quantification not necessarily clinically relevant ○ Applications beyond human evaluation not yet approved/used for clinical management ○ AI intransparent (“black box”) ○ Regulatory oversight challenges with self-modifying (adaptive) AI as algorithm/performance not constant over time
WSI-teaching	○ Digital images for presentation and exams readily available ○ Remote teaching and self-study ○ Increased student motivation, modern appeal	None
Costs and efficiency gains ○	○ Work time saved through faster turnaround times ○ Decreased auxiliary techniques (less immunohistochemistry) ○ Decreased physical slide-transfer costs	DP implementation and maintenance and storage costs add to current fixed costs if productivity gains remain unrealized (fixed work contracts) ○ Dual infrastructure costs (workstations and microscopes if kept) ○ Glass and digital storage still generally deemed necessary ○ Technical expert knowledge for hardware acquisitions needed

5 Ways Quantitative Digital Pathology Can Add Value to Immuno-Oncology R&D

Confidence building proof of mechanism data

- Quantitative histopathology can be utilized, for instance, to demonstrate that organization of a designated spot inhibitor or blend treatment brings about expanded quantities of CD8 T cells in practical tumor tissue and that this connects with in general decreases in tumor volume.

Evaluate multiple cells and biomarkers on one tissue section

- Advances in multiplex immunohistochemistry (IHC) and immunofluorescence (IF) procedures joined with novel picture investigation shading deconvolution calculations imply that it is currently conceivable to not just all the while evaluate the presence up to 4 cell types or biomarkers inside oncology tissue yet additionally to give information on the dispersion and co-localization of various and biomarkers on entire tissue segments.

Quantify immune cell infiltration or proximity to a tumor border

- Advancing the penetration of dynamic insusceptible cells into the tumor microenvironment is a significant element of numerous immunotherapies. Concentric groups set inside the Tumor-Stroma line at pre-decided distances, permit the evaluation of insusceptible cells inside characterized groups inside a tumor. This methodology can help affirm the instrument of activity of treatments that are intended to build the penetration of immune cells into tumor from encompassing tissue.

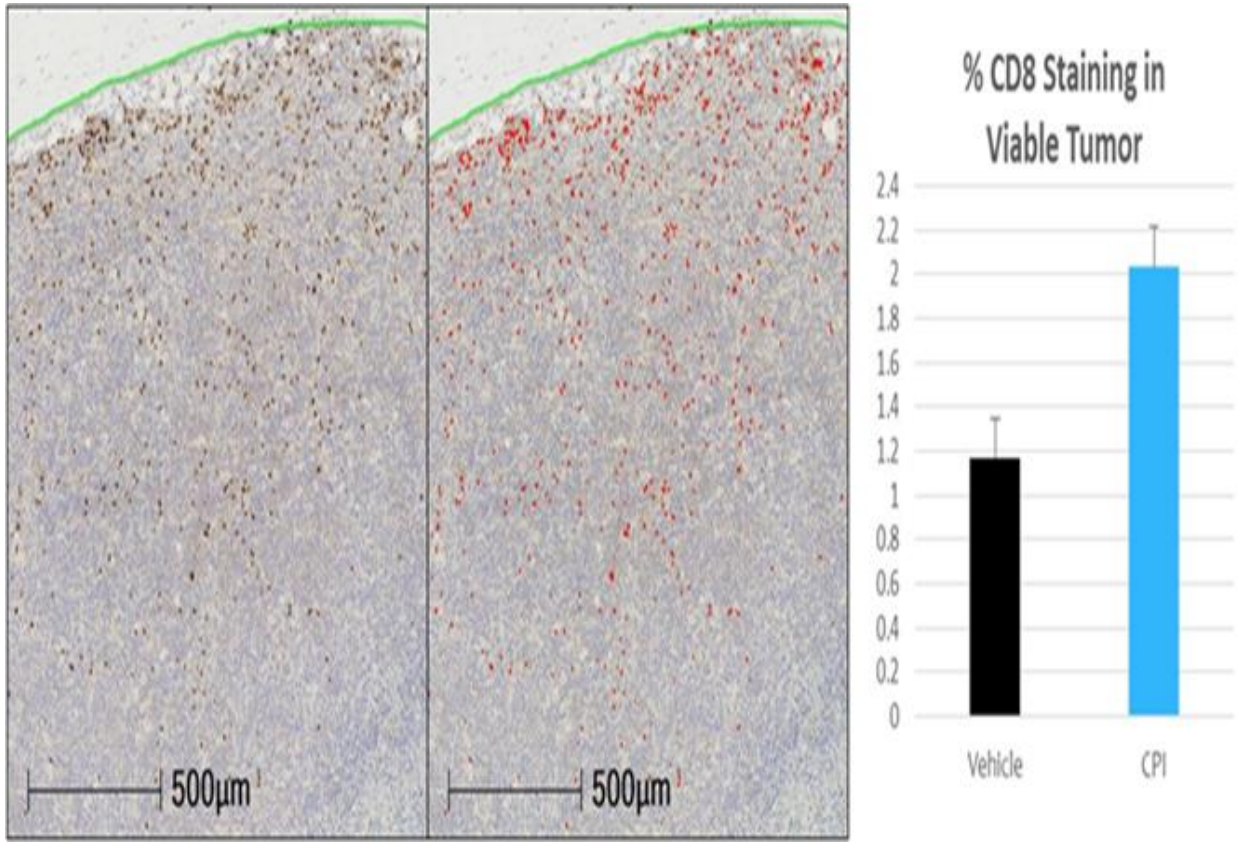
Determine cell-cell interactions within tumor microenvironment

- Differentially staining explicit cell types permits the measurement of the spatial setting between singular cells and their closest neighbor inside tumor tissue. This methodology can help affirm the instrument of activity of treatments that are intended to improve or lessen the collaboration between explicit cell types inside tumor tissue.

Interpret data in context of its Tumor Microenvironment

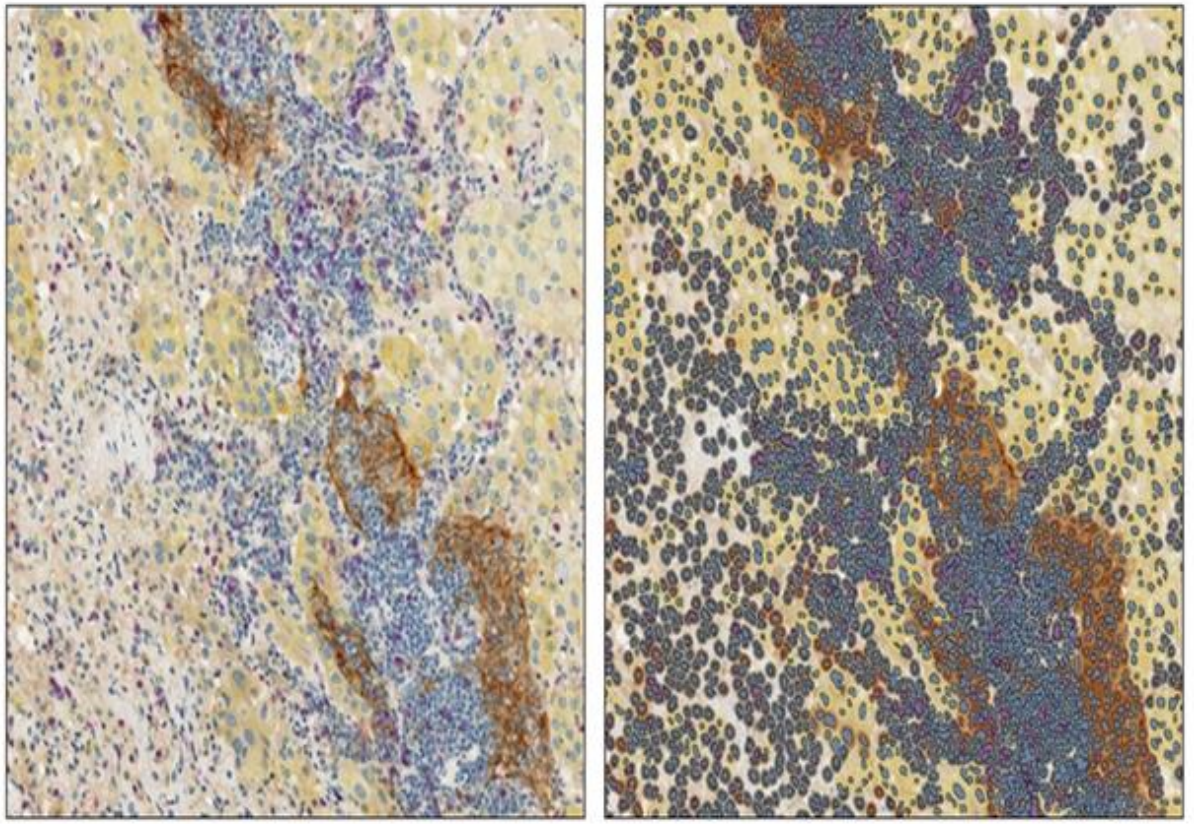
- Mulling over morphological highlights such as, practical tissue versus necrotic substance, rejection of xenograft has tissue from examination of entire areas, or exact division of tumor and stroma regions of interest (ROI) can essentially improve the quality and understanding of remedial reaction across entire tissue segments.

Confidence building proof of mechanism data



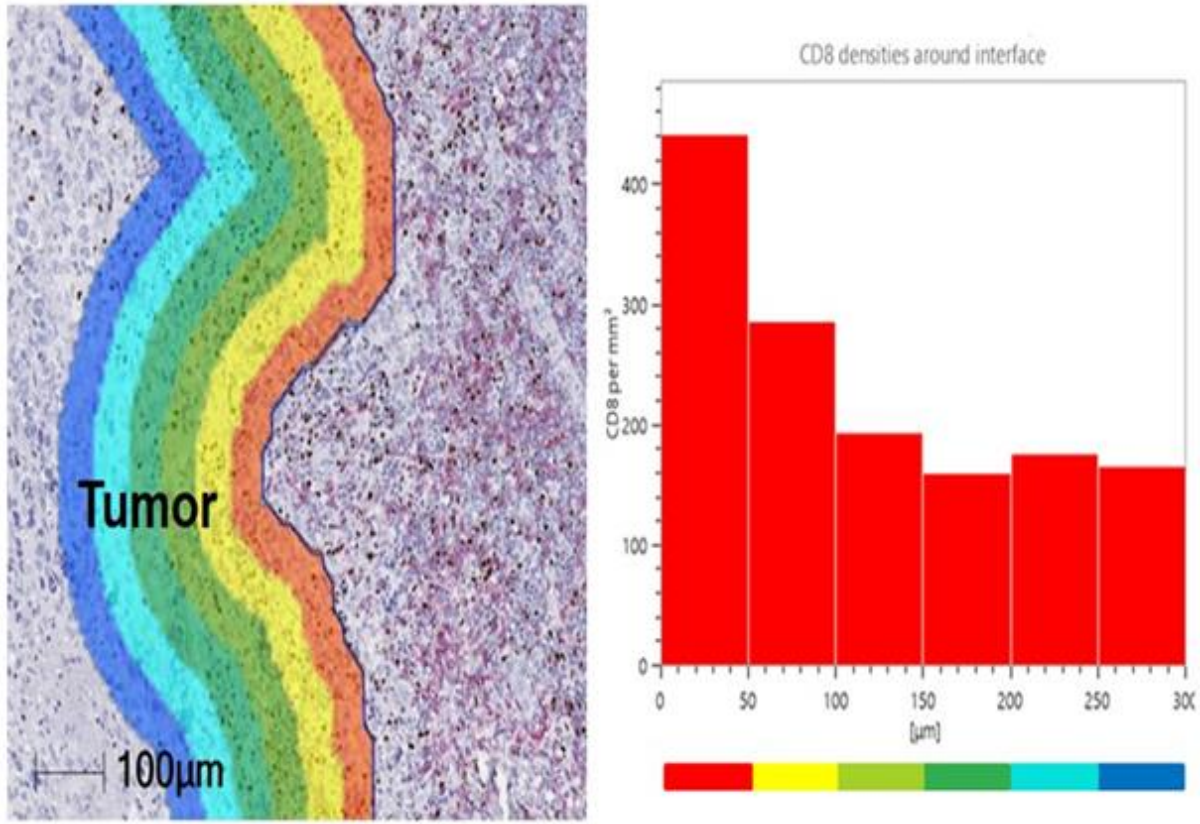
Left) High magnification of CD8 IHC staining (brown) in viable tumor
Middle) Image analysis of CD8 stain area (red overlay) within viable tumor
Right) Example Vehicle versus Checkpoint inhibitor (CPI) group data for CD8 content in viable tumor from a xenograft study.

Evaluate multiple cells and biomarkers on one tissue section



Left: IHC Multiplex stained tumor tissue showing CD8 immune cells (purple), DP-L1 staining (brown), Pan-CK (yellow) and haematoxylin (blue)
Right: Image analysis detection of CD8 (red), DP-L1+ cells (dark brown), Pan-CK tumor cells (yellow) and DP-L1+/Pan-CK+ tumor cells (light brown)

Quantify immune cell infiltration or proximity to a tumor border



Left: Application of 6 x 50µm infiltration bands from tumor boundary into tumor. CD8 (red) and FoxP3 (brown) via IHC.
Right: Number of CD8 cells per mm2 in tumor, per infiltration band from tumor border interface

Determine cell-cell interactions within tumor microenvironment

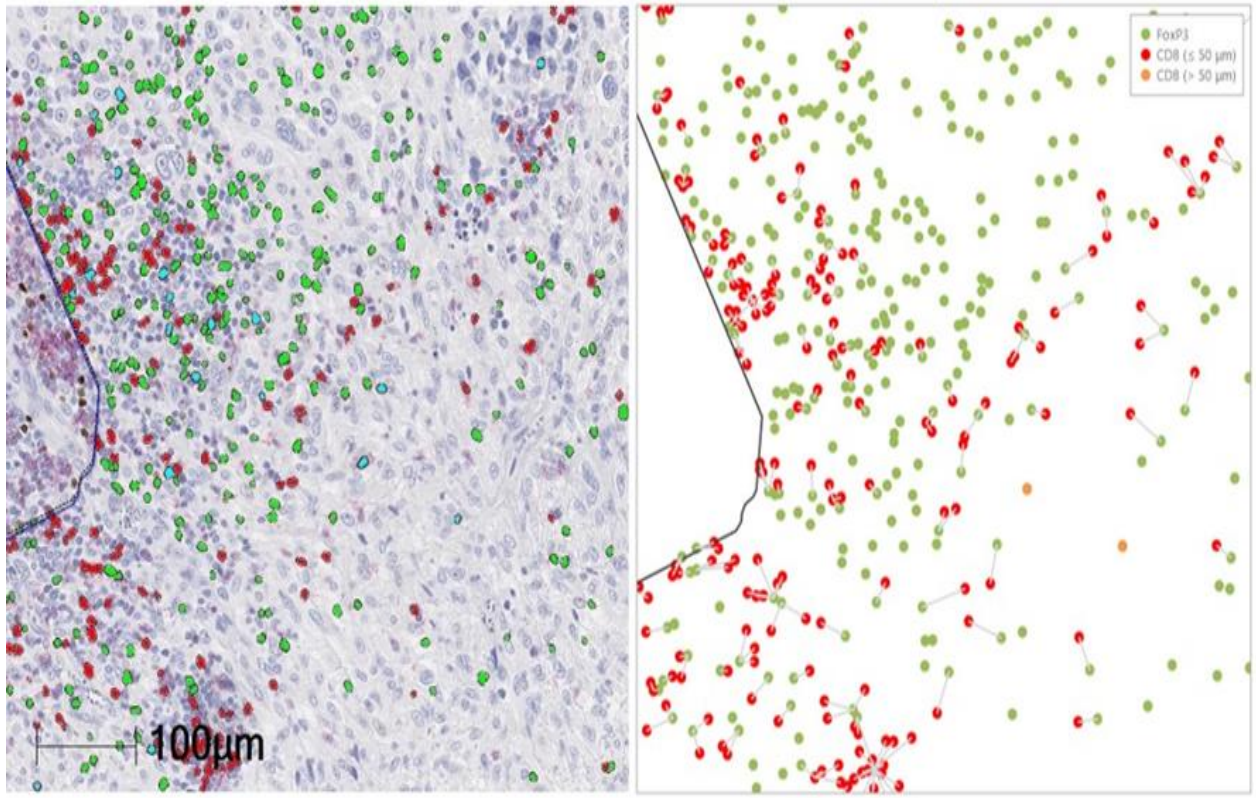


Figure 3.5 1-Left: CD8+ cells (red overlay) and FoxP3+ nuclei (green overlay) detected by image analysis
Right: Spatial distribution showing CD8+ cells ≤50µm from a FoxP3+ nuclei (red) or >50µm from a FoxP3+ nuclei (orange)

Interpret data in context of its Tumor Microenvironment

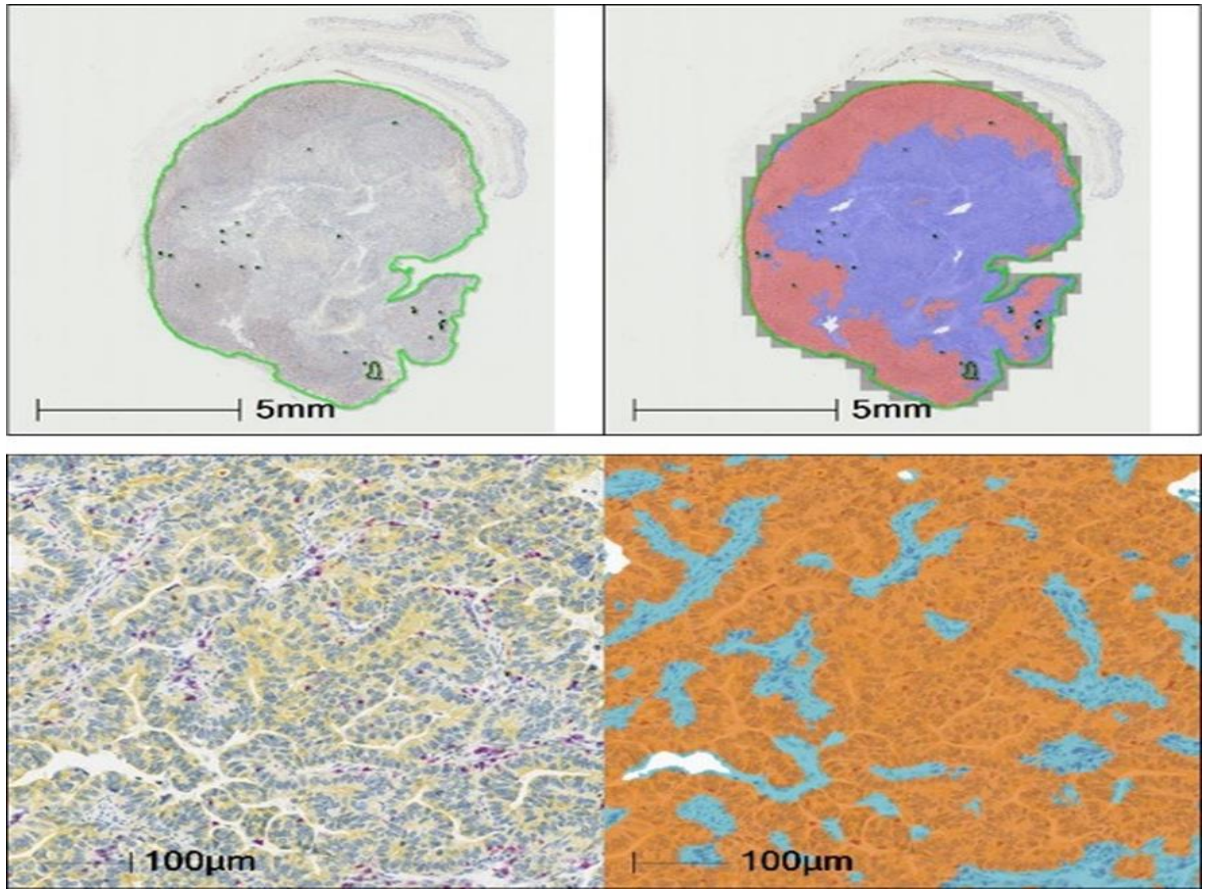


Figure 3.6 1-Top images: IHC stained whole tissue section showing annotation of tumor (green outline) excluding host tissue and further segmentation of viable (red overlay) and necrotic content (purple overlay) for ROI cell analysis
Bottom images: Image analysis classification of tumor (orange overlay) and stroma (blue overlay) ROI within multiplex IHC stained tissue

CONCLUSION

- DP undoubtedly holds great potential for routine histopathology in the near future. DP has shown exciting results for primary histopathological diagnoses, even more so with AI applications now becoming embedded into the digital reporting work-flow.
- Additionally, as more of the image evaluation algorithms & the computer-aided diagnostic tools are advanced & authenticated for the medical usage, pathologists can be more resourceful, accurate and reproducible in the quantification of prognostic biomarkers.
- The two key features that will aid facilitate the usage of DP in medical routines are the usage of routine practices which are standard & the validation & the development of the image analysing tools.
- Accuracy & reproducibility are improved in WSI by applying digital analysis algorithms to quantify image analysis data.


Thank
you