Unlashing the Power of Digital Pathology and Artificial Intelligence for Precision Medicine

Marilyn Bui, MD, PhD
About the Presenter

• Senior Member/professor of Pathology, Scientific Director of Analytic Microscopy Core, President of Medical Staff and Cytopathology Fellowship Program Director at the Moffitt Cancer Center [https://moffitt.org](https://moffitt.org) in Tampa, Florida

• Chair of the College of American Pathologists (CAP) [www.cap.org/](http://www.cap.org/) Guidelines Committee Expert Panel for Quantitative Image Analysis of HER2 Immunohistochemistry for Breast Cancer. Vice chair of the CAP Digital Pathology Committee

• President-elect of the Digital Pathology Association [https://digitalpathologyassociation.org/](https://digitalpathologyassociation.org/)
Objectives

• Review of the revolution of digital pathology (DP) and its impact on precision medicine
• Discuss lessons learned and challenges
• Looking forward to future opportunities and collaboration
Digital Pathology (DP)

One of the most promising fields of digital medicine

- Integrated pathology informatics
- Transform pathology data into clinically actionable knowledge
- Connectivity & accessibility
- Image analysis, artificial intelligence and automation
- Improved quality & efficiency
Digital Pathology & Artificial Intelligence

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A patient’s medical journey begins with their diagnosis...

Pathologists provide forecast of Diagnosis, Prognosis & Prediction of therapeutic response.
Artificial Intelligence - The Third Revolution in Pathology

The Microscope Was Once A “Disruptive” Technology

“The use of the microscope in pathological investigations is an art so difficult that none but those who have especially cultivated it (and for a long time) can depend on it for correctness. On this account, it can never become employed in ordinary practice.”

Alfred Stille, 1848 – Elements of General Pathology

Artificial Intelligence - The Third Revolution in Pathology

Manuel Salto-Téllez, Perry Maxwell, Peter Hamilton

First published: 01 October 2018 | https://doi.org/10.1111/his.13760
Hereby we stress the importance of certified pathologists having learned from the experience of previous revolutions and be willing to accept such disruptive technologies, ready to innovate and actively engage in the creation, application and validation of technologies and oversee the safe introduction of AI into diagnostic practice.
Digital pathology is not just the transfer of histopathological slides into digital representations. The combination of different data sources (images, patient records, and *omics data) together with current advances in artificial intelligence/machine learning enable to make novel information accessible and quantifiable to a human expert, which is not yet available and not exploited in current medical settings.

**Application**
- Detection
- Quantification
- Classification
- Prognosis
- Prediction

**Materials & Methods**
- HE, special stain, IHC, fluorescence, live cells, etc.
- Image analysis through machine learning, deep learning/artificial intelligence

**Desirable Results**
- Improved quality & efficiency
- Pathology data → clinically actionable knowledge

**Augmented Pathologist**

**Explainable Artificial Intelligence** in Digital Pathology by Holzinger, Malle, Kieseberg, Roth, Muller, Reihs, Zatloukal

Deep Learning in Breast Pathology

Automated classification of patients with metastatic breast cancer in lymph node


2. Peter Bandi, Oscar Geessink, Quirine Manson, et al. From detection of individual metastases to classification of lymph node status at the patient level: the CAMELYON17 challenge. IEEE-TMI (Early Access) DOI: 10.1109/TMI.2018.2867350

Downloading the data set

CAMELYON16 and CAMELYON17 data sets are open access and shared publicly on GigaScience, Google Drive and on Baidu Pan.
A deep learning approach for learning survival directly from histological images and created a unified framework for integrating histology and genomic biomarkers for predicting time-to-event outcomes.

Systematically evaluated the prognostic accuracy of this approaches in the context of the current clinical standard based on genomic classification and histologic grading of gliomas.

This approach rivals or exceeds the accuracy of highly trained human experts in predicting survival.

Improving the accuracy and objectivity of grading will directly impact patient care.
Deep Learning in Lung Cancer

Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning

Nicolas Coudray, Paolo Santiago Ocampa, Theodore Sakellaropoulos, Navneet Narula, Matija Snuderl, David Fenyo, Andre L. Moreira, Narges Razavian, and Aristotelis Tsinigkos

Visual inspection of histopathology slides is one of the main methods used by pathologists to assess the stage, type and subtype of lung tumors. Adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) are the most prevalent subtypes of lung cancer, and their distinction requires visual inspection by an experienced pathologist. In this study, we trained a deep convolutional neural network (inception v3) on whole-slide images obtained from The Cancer Genome Atlas to accurately and automatically classify them into LUAD, LUSC or normal lung tissue. The performance of our method is comparable to that of pathologists, with an average area under the curve (AUC) of 0.97. Our model was validated on independent datasets of frozen tissues, formalin-fixed paraffin-embedded tissues and biopsies. Furthermore, we trained the network to predict the ten most commonly mutated genes in LUAD. We found that six of them—STK11, EGFR, FAT1, SETBP1, KRAS and TP53—can be predicted from pathology images, with AUCs from 0.733 to 0.856 as measured on a held-out population. These findings suggest that deep-learning models can assist pathologists in the detection of cancer subtype or gene mutations. Our approach can be applied to any cancer type, and the code is available at https://github.com/ncoudray/DeepPATH.
Assessment of PD-L1 Expression & Immune Cell Infiltrates

Precision immunoprofiling by image analysis and artificial intelligence

Viktor H. Koelzer, Korsuk Sirinukunwattana, Jens Rittscher, Kirsten D. Mertz

Received: 15 May 2018 / Revised: 6 November 2018 / Accepted: 9 November 2018

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Multiplex IHC for Clinical Trials

Assessment of Immune Cells

Multiplex IHC Stained Section

 Courtesy of Susan McCarthy of Moffitt Cancer Center using Vectra in a CLIA lab for clinical trials
Barriers to DP Adoption

- Regulatory
- Financial
- Technical
- Cultural
• Leading digital pathology companies have recently received **FDA approval** for whole slide imaging system for primary diagnosis in US or **CE certification** for routine pathology applications in the European Union under the In vitro diagnostic medical devices directive.

References:
• College of American Pathologists (CAP) set general guidelines on how to validate the imaging system to ensure the consistency of diagnosis made by pathologists using the systems.
Breaking Financial Barriers

~ 12-13% (published) efficiency gain at pathologist level
~ Saving on retrieval of archived slides
~ Merger of departments/labs with flexible pathologist availability
~ Reduced turn around time changes patient pathways
  • reducing visits and in-patient time
  • better more efficient use of resources
~ Facilitates review improving diagnostic accuracy

Can Digital Pathology Result In Cost Savings? A Financial Projection For Digital Pathology Implementation At A Large Integrated Health Care Organization

Jonhan Ho, Stefan M. Ahlers¹, Curtis Stratman², Orly Aridor³, Liron Pantanowitz⁴, Jeffrey L. Fine⁵, John A. Kuzmishin⁶, Michael C. Montalto⁷, Anil V. Parwani⁸

Future-proofing pathology part 2: building a business case for digital pathology

Bethany Jill Williams¹, ², David Bottoms³, David Clark⁴, Darren Treanor¹, ²
Breaking Technical Barriers

- Image quality
- Open software solutions
  - Open to many scanners
  - Open to many image analysis suites
- System (LIS/LIMS) integration
- Speed, file storage and IT infrastructure
Breaking Technical Barriers

- **Integrating the Health Care Enterprise (IHE) Pathology and Laboratory Domain (PALM)**
  An initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information; an international standards organization that bundles existing standards into profiles that solve particular medical communication problems.

- **Digital Imaging and Communication in Medicine (DICOM)**
  The standard file format definition and communication profile for radiological and many other medical images.

- **IHE/PLAM & DICOM collaborative digital pathology initiative starting in 2017 to create interoperability for digital pathology**
Breaking Cultural Barriers

Proven Phased Adoption Strategy

Phase 1
Planning

Phase 2
Scan Lab
On-line

Phase 3
Retrospective
Scanning

Phase 4
Review/
Consult Scans

Phase 5
Primary
Diagnosis

over ~ 18-24 months
Lessons Learned

Learning from early adopters who publish results

Optimizing throughput in the world’s largest pathology imaging facility
Authors: Lloyd MC, Kellough D, Shanks T, Deshpande A, Singhal S, Parwani A

Sectioning Automation to Improve Quality and Decrease Costs for a High-Throughput Slide Scanning Facility
Authors: Cuddihy M, Shulgay T, Ferree L, Krueger G, Mack D, Pietryka K, Parwani A, Gill T, Lloyd MC

Computational Detection of Mitotic Figures using A Fusion of Deep Learning and Domain-Based Approaches
Authors: Harding D, Verma N, Mohammadi A, Monaco J, Lloyd MC, Tozbikian G, Li Z, Parwani A
• The digitization of pathology in WSI will provide a huge source of data that will ultimately lead to computer-assisted diagnostics.
• The integration of all the various data obtained in laboratories is the future of pathology.
• The pathologist is a trained physician who has expertise in making the correct diagnosis, determining the likely prognosis, and, with the additional information derived from multiple tests, providing a consultative opinion about treatment approaches.
• As laboratory testing plays an increasing role in the era of personalized medicine, the role of the pathologist increases, and the need for consolidated interpretive reporting becomes critical.
• The depth of knowledge required to integrate these various ancillary technologies demands the insight of subspecialty pathology and promotes a critical role for pathologists in the implementation of precision medicine.
Opportunities

- Workflow efficiency; review current & priors cases instantly
- Telepathology and case sharing

- Image analysis

Lloyd, Monaco ASCO 2018
Integrated Digital Pathology Solutions

FROM PHYSICAL WORKFLOW

Generalists

Over Loaded

Under Loaded

Dispersed, generalist

TO DIGITAL WORKFLOW

Level Loaded

Patient

Specialization

Optimised & patient centric
What’s next?

Developing value-added tools

- Cancer finding tool
- Region of interest finder tool
- Mitotic count tool
- Pre-screening of IHC slides with quantitative scores
- Bug finder (e.g. mycobacteria)
- More accurate, faster measurements
- Tumor grading tools
- Application of image analysis to routine practice
- Image capture and export to the report
Opportunities: The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA)

- A collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI).
- **Free public dataset** with comprehensive, multi-dimensional maps of the key genomic changes in 33 types of cancer.
- Comprising more than two petabytes of genomic data.
- This **genomic information** helps the cancer research community to improve the prevention, diagnosis, and treatment of cancer.

https://wiki.nci.nih.gov/display/TCGA/Introduction+to+TCGA
http://cancerdigitalslidearchive.net/
Opportunities: TCGA Data

PanCancer insights from The Cancer Genome Atlas: the pathologist’s perspective

Lee AD Cooper†, Elizabeth G Demicco**, Joel H Saltz†, Reid T Powell†, Arvind Rao†, and Alexander J Lazar†

TCGA Tissue Procurement

TCGA Overview
Future Collaborations

Future clinical demands will be best met by

• Dedicated research at the interface of pathology and bioinformatics, supported by professional societies
• Integration of data sciences and digital image analysis in the professional education of pathologists.
Preanalyticals Affect H&E
Preanalyticals Affect Immunostains
Preanalyticals Affect H&E and Immunostains

HISTOQIP

HQIP Whole Slide Image Quality Improvement Program  HQWSI

<table>
<thead>
<tr>
<th>Stain/Tissue</th>
<th>Program Code</th>
<th>Challenges per Shipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E - Breast resection</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Lung resection</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Breast needle core biopsy</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Prostate needle core biopsy</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Colon resection</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Kidney resection</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Colon biopsy</td>
<td>■</td>
<td>1</td>
</tr>
<tr>
<td>H&amp;E - Skin punch biopsy</td>
<td>■</td>
<td>1</td>
</tr>
</tbody>
</table>

Program Information
- Participant laboratories may submit up to four stained coverslipped glass slides and upload their scanned whole slide images per mailing
- Two shipments per year

2019 Surveys and Anatomic Pathology Education Programs

College of American Pathologists Laboratory Quality Solutions
• The Centers for Medicine & Medical Services (CMS) regulates all lab testing performed on humans in US through the Clinical Laboratory Improvement Amendments (CLIA)

• Proficiency Testing (PT) is one way that CMS monitors laboratories performance

• CAP Proficiency Testing (PT) specimens must be tested with the laboratory’s regular workload, using routine methods, and testing the PT specimens the same number of times it routinely tests patient specimens.
Analyticals Affect Immunostain Interpretation

- CAP ER/PR and HER2 Immunohistochemistry (IHC) Tissue Microarray (TMA) Survey

One TMA for ER IHC containing 10 samples
PM2-02-2017-A
Stained at Moffitt Cancer Center (SP1 with antigen retrieval)
http://capatholo.gy/TMA1

One TMA for HER2 IHC containing 10 samples
HER2-01-2017-A
Stained at Moffitt Cancer Center (4B5 PATHWAY)
http://capatholo.gy/TMA2
A good quantitative image analysis (QIA) algorithm produces accurate, precise and reproducible result.
In conclusion, the system for DIA evaluated here was in most aspects a superior alternative to manual biomarker scoring. It also has the potential to reduce time consumption for pathologists, as many of the steps in the workflow are either automatic or feasible to manage without pathological expertise.

Table 2 Molecular ‘intrinsic’ breast cancer subtypes and surrogate definitions by immunohistochemical profile

<table>
<thead>
<tr>
<th>Intrinsic subtype</th>
<th>Surrogate IHC classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER ≥ 1% and/or PR ≥ 20% and HER2 ‘negative’ and Ki67 ‘low’</td>
</tr>
<tr>
<td>Luminal B</td>
<td>1. ER ≥ 1% and/or PR ≥ 20% and HER2 ‘negative’ and Ki67 ‘high’ or ER ≥ 1% and/or PR &lt; 20% and HER2 ‘negative’. Any Ki67 or ER ≥ 1% and PR ≥ 1% and HER2 ‘positive’. Any Ki67</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>ER &lt; 1% and PR &lt; 1%. HER2 ‘positive’. Any Ki67</td>
</tr>
<tr>
<td>Basal-like</td>
<td>ER &lt; 1% and PR &lt; 1%. HER2 ‘negative’. Any Ki67</td>
</tr>
</tbody>
</table>

% = Proportion of tumor cells stained with the respective biomarker. ‘Positive’ and ‘negative’ = as defined by the American Society of Clinical Oncology and College of American Pathologists recommendations for human epidermal growth factor receptor 2-testing in breast cancer. High’ and ‘low’ = as defined by each laboratory’s own reference data, with threshold generally in the range of 14–29%. 10
HER2 Quantitative Image Analysis (QIA)

- QIA has been shown to improve consistency and accuracy of interpretation than manual scoring by pathologists, but has not gained widespread acceptance.
  
  In 2016, 183 (22.1%) of the 826 laboratories enrolled in the CAP HQIP-A mailing, reported using QIA.

- While the ASCO/CAP HER2 testing guidelines addressing the key pre-analytical and IHC related issues, there is a need of guideline for HER2 IHC QIA.

**CAP QIA Guideline Scope:**
- to provide recommendations for improving accuracy, precision and reproducibility in the interpretation of HER2 IHC where QIA is employed.
CAP Center Guideline Methods

1. Submit and Select Ideas
2. Determine Scope and Form Workgroup
3. Research and Review Evidence/Draft Recommendations
4. Solicit Comment
5. Complete Recommendations
6. Review and Approve
7. Publish and Implement
8. Maintain
1. What equipment validation and daily performance monitoring is needed?

2. What training of staff and pathologists is required? What are the competency assessments needs over time?

3. How does one select or develop an appropriate algorithm for interpretation?

4. How does one determine the performance of the image analysis?

5. How should image analysis be reported?

**11 recommendations**
- 7 recommendations (based on laboratory accreditation requirements)
- 4 expert consensus opinions
CAP Helps Pathologists and Laboratories Adopting DP

• Digital Pathology Committee
• Pathology and Laboratory Quality Center Committees

*CAP Evidence-Based Guidelines* –
- Revisions to whole slide imaging validation guidelines
- Quantitative imaging analysis of HER2 immunohistochemistry for breast cancer guidelines

**Improve diagnostic and treatment decision making**

- Current Guidelines
- Upcoming Guidelines
CAP Helps Pathologists and Laboratories Adopting DP

**Digital Pathology Committee**

**Charge:**
To advance the adoption of digital pathology within the CAP and to serve as a respected resource for information and education for pathologists, patients, and the public on the practice and science of digital pathology.
Updated CAP WSI validation guidelines.


Clinical Guidelines for Telepathology
August 2014

http://www.jpathinformatics.org/article.asp?issn=2153-3539;year=2014;volume=5;issue=1;spage=39;epage=39;aulast=Pantanowitz
Whole Slide Imaging (WSI) for Primary Diagnosis: Is Your Practice Prepared for the Digital Future?

US Food and Drug Administration Approval of Whole Slide Imaging for Primary Diagnosis

A Key Milestone Is Reached and New Questions Are Raised

Andrew J. Evans, MD, PhD; Thomas W. Bauer, MD, PhD; Marilyn M. Bui, MD, PhD; Toby C. Cornish, MD, PhD; Helena Duncan, BBA; Eric E. Glaissy, MD; Jason Hipp, MD, PhD; Robert S. McGee, MD, PhD; Doug Murphey, MT (ASCP); Charles Myers, MD; Dennis G. O’Neill, MD; Anil V. Parwani, MD, PhD; B. Alan Rampy, DO, PhD; Mohamed E. Salama, MD; Liron Pantanowitz, MD

• April 12, 2017 marked a significant day in the evolution of digital pathology in the United States, when the US Food and Drug Administration announced its approval of the Philips IntelliSite Pathology Solution for primary diagnosis in surgical pathology. Although this event is expected to facilitate more widespread adoption of whole slide imaging for clinical applications in the United States, it also raises a number of questions as to the means by which pathologists might choose to incorporate this technology into their clinical practice. This article from the College of American Pathologists Digital Pathology Committee reviews frequently asked questions on this topic and provides answers based on currently available information.

http://capatholo.gy/2Agehmu
Implementation of Whole Slide Imaging for Clinical Purposes

Issues to Consider From the Perspective of Early Adopters

Andrew J. Evans, MD, PhD; Mohamed E. Salama, MD; Walter H. Henricks, MD; Liron Pantanowitz, MD

Context.—There is growing interest in the use of digital pathology, especially whole slide imaging, for diagnostic purposes. Many issues need to be considered when incorporating this technology into a clinical laboratory. The College of American Pathologists (CAP) established a Digital Pathology Committee to support the development of CAP programs related to digital pathology. One of its many initiatives was a panel discussion entitled “Implementing Whole-Slide Imaging for Clinical Use: What to Do and What to Avoid,” given for 3 years at the CAP annual meetings starting in 2014.

Objectives.—To review major issues to consider when implementing whole slide imaging for clinical purposes as covered during the panel discussion.

Design.—The views expressed and recommendations given are based primarily on the personal experience of the authors as early adopters of this technology. It is not intended to be an exhaustive review of digital pathology.

Results.—Implementation is best approached in phases. Early efforts are directed toward identifying initial clinical applications and assembling an implementation team. Scanner selection should be based on intended use and budget. Recognizing pathologist concerns over the use of digital pathology for diagnostic purposes, ensuring adequate training, and performing appropriate validation studies will enhance adoption. Once implemented, the transition period from glass slide to image-based diagnostics will be associated with challenges, especially those related to a hybrid glass slide–digital slide workflow.

Conclusions.—With appropriate preparation, planning, and stepwise implementation, whole slide imaging can be used safely and reliably for frozen sections, consultation, quality assurance, and primary diagnosis.

Hosted FDA at DPA PathVisions

DPA formed industry sub-committee

DPA pathologists meet with FDA to discuss risk/benefit,

DPA hired external FDA regulatory firm to counsel DPA

DPA establishes unified response to Draft guidance

DPA actively engage FDA on classification clarity

DPA clarifies special controls

FDA holds public hearings, class III designated (2009)

First DeNovo Clearance of WSI for Primary Dx

FDA reverse class III designation and decide on de novo pathway (class II)
Next Task: Regulatory Path for AI

Facilitate bringing safe and state-of-the-art pathology algorithms to the market in an efficient way.

https://nciphub.org/groups/wsi_working_group
DPA, in collaboration with NSH, developed the first ever certificate program for digital pathology

174 Course Registrations
In 8 months!

NOW AVAILABLE!
DPA in Interoperability with DICOM

- DPA hosted the first Connectathon at Pathology Visions 2017
- Formation of DICOM & Standards Task Force

“We learned more in this one event than we did in the past 7 years”

Dr. David Clunie, DICOM WG 26 Co-chair
DPA in Education and Awareness

Publication & White Papers

• Abstracts of all Pathology Visions presentation are published in the *Journal of Pathology Informatics* since 2017.
• Member publication posting on DPA website is available per request.
• Previous white paper presentations are on DPA website.
• Various new white papers are in progress.

Webinars & Blogs

• DPA members have access to all archived webinars.
• DPA members are welcome to post blogs.
SAVE THE DATE

2019 PATHOLOGY VISIONS

Celebrating the 10 Year Anniversary of the Digital Pathology Association!

Keynote Presenter:
Anil Parwani, MD, PhD, MBA | Ohio State University Wexner Medical Center

October 6-8
Hyatt Regency Orlando Orlando, Florida
Conclusions

- Digital pathology and artificial intelligence are here to stay and will continuously transform the delivery of precision medicine.
- Collaboration of pathologists, scientists and industry are important to move the field forward in an impactful way.
- Each individual can make a difference.
Any Questions?

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https://moffitt.org/providers/marilyn-bui/

@DrBuiPathology

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Acknowledgements

- Drs. Eric Glassy, Mark Lloyd and Michael Montalto for slide sharing
Thank you!

http://moffittcourage.org/#story-973ce228-f773-11e6-9947-22000ae60fb9