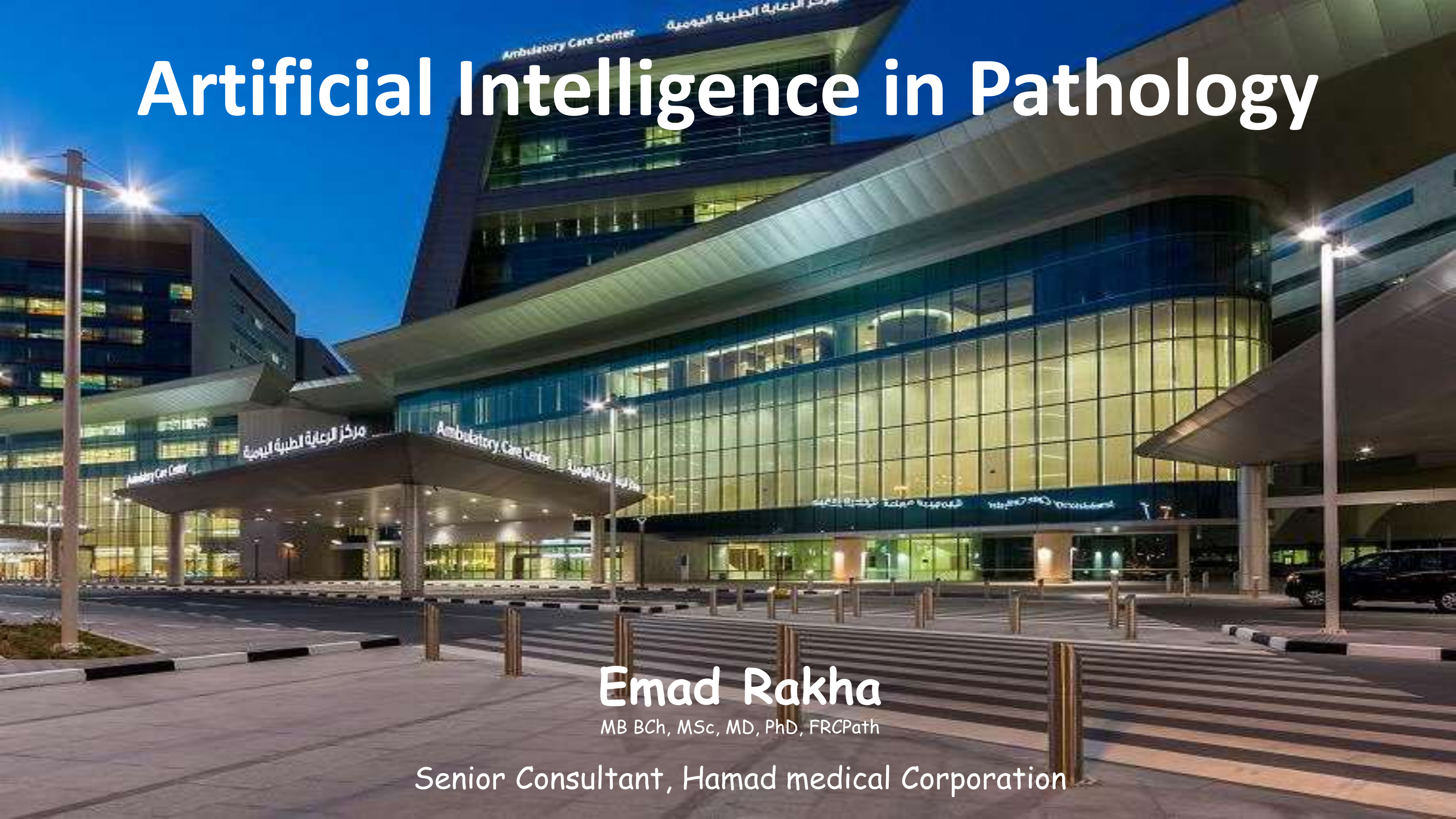
Emad Rakha
HMC, Qatar

Emad Rakha is Senior Consultant Pathologist at Hamad Medical Corporation and Professor of Breast Pathology at the University of Nottingham. Prof Rakha is the co-chair of the UK External Quality Assurance (EQA) Scheme and the leader of the Nottingham Breast Pathology Research Group (BPRG), which has a national and international reputation for its research in diagnosis, classification of breast diseases, and evaluation of clinical outcomes of breast cancer. Emad authored over 500 publications in peer review journals and wrote more than 40 books and book chapters. He has written the UK national HER2 guidelines and has contributed to other breast pathology national guidelines and textbooks including the WHO Blue Book, Fletchter and Dabb's Books. He is a member of several committees including the UK BIG18 group, ISBP and ABP. He runs the Nottingham Breast Pathology Masterclass and regularly contributes to other breast pathology training courses worldwide and lectures at national and international courses and scientific meetings.

Artificial Intelligence in Pathology



Emad Rakha

MB BCh, MSc, MD, PhD, FRCPath

Senior Consultant, Hamad medical Corporation

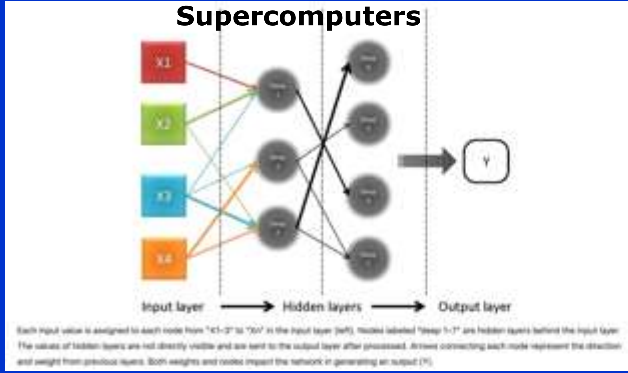
Disclosure Statement

I make the following declaration in relation to this CPD Activity :

- There is NO Conflict of Interest.
- There is no plagiarism or copyright infringement.
- The content is balanced and free of bias, either commercial or non-commercial.

* AI is the intelligence of machines or software, as opposed to the intelligence of humans (computational achievement of goals)

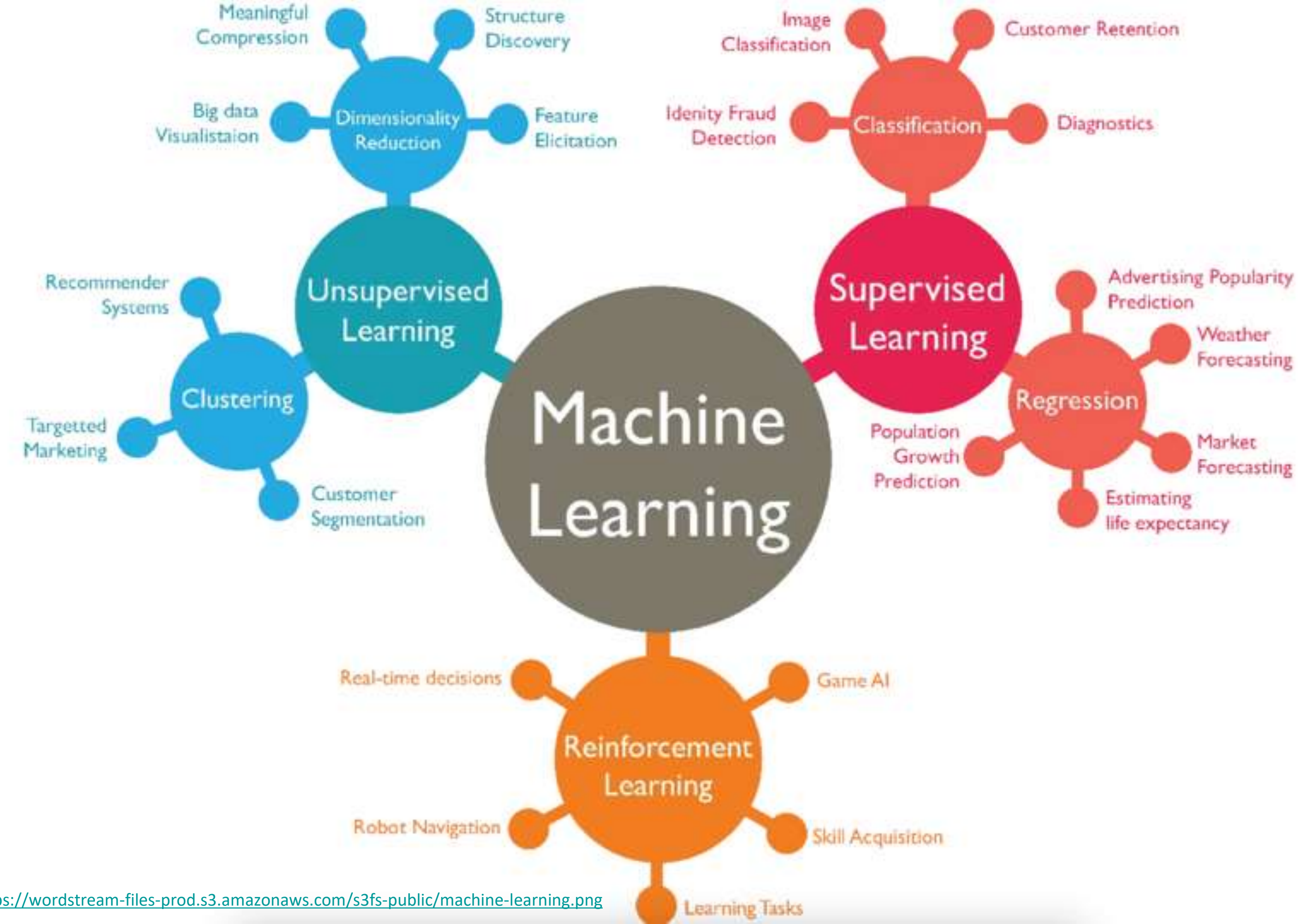
* AI is different from existing mathematical methods by the added value of learning from the data (self-learning) to generate learned outcome and prediction models (big data processing and learning to achieve goals)



* *The final outcome is called "algorithms"*

* AI is fast and can perform certain tasks better than humans.

*AI technology is widely used in many fields



https://wordstream-files-prod.s3.amazonaws.com/s3fs-public/machine-learning.png

Terms

* AI, machine learning, deep learning (Artificial neural network, convolutional neural network), NLP ..etc

* Digital pathology & Computational pathology,

* Big data mining, data lakes, supercomputers …..etc

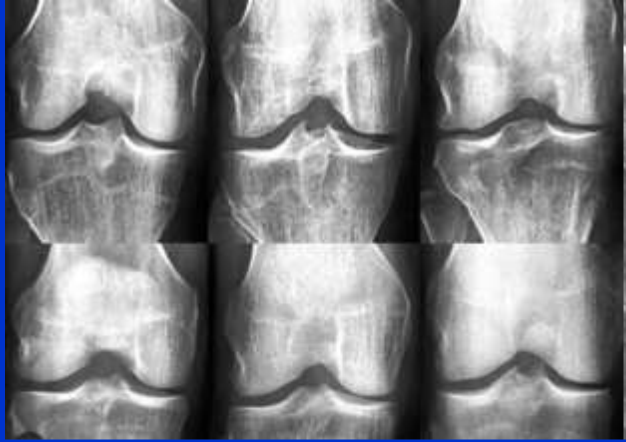
* Computer vision, compared to image analysis and processing, is a branch of AI, that focuses on learning, making inferences and taking actions based on visual inputs

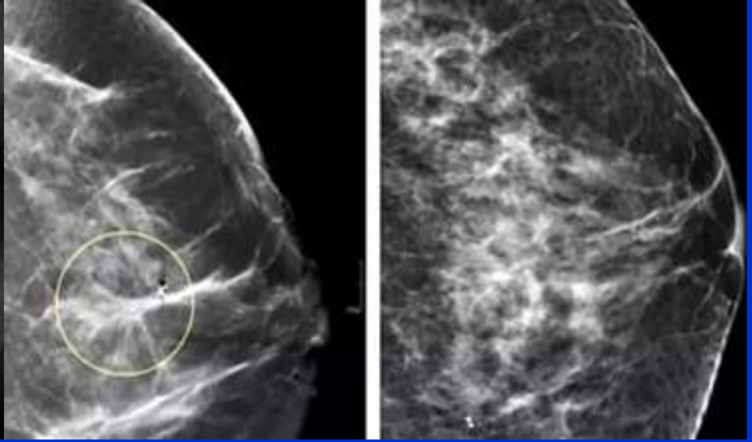
Laboratory Investigation **volume 101**, pages412–422 (2021)

* AI is increasing used in the healthcare system
    - Managing healthcare data and other big data
    - Improving medical diagnosis
    - Performing robotic medical intervention
    - Automation and Nature Language processing

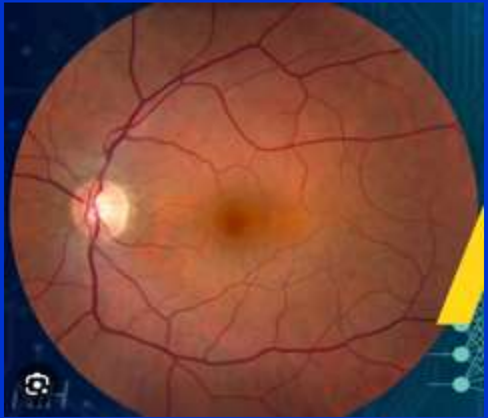
* AI applications in medical field attracted more attention in recent years by dealing with *medical images* (computer vision): in radiology, pathology, ophthalmology, dermatology…etc

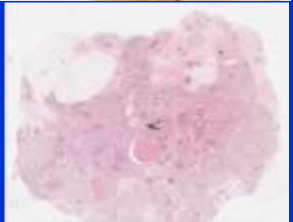
* Pathology: Require digitalization of slides (WSI)






Hold ~4 inches (10 cm) away from the affected area





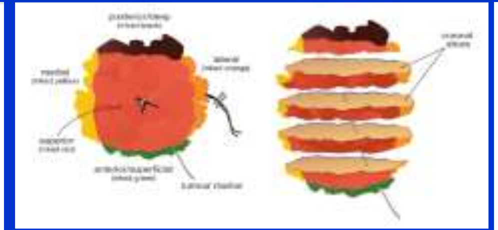
AI in pathology (*computational pathology*)

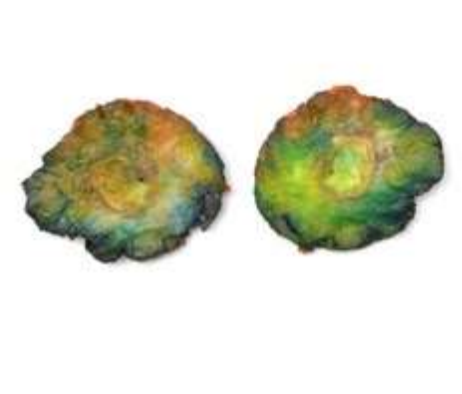
* Computer technology and AI are already used in many areas in pathology: digital dictation (dragon)

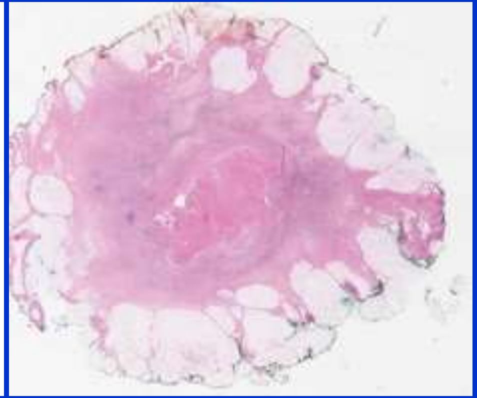
* AI algorithms can also be used to facilitate specimen pathways, preparation, processing and reporting

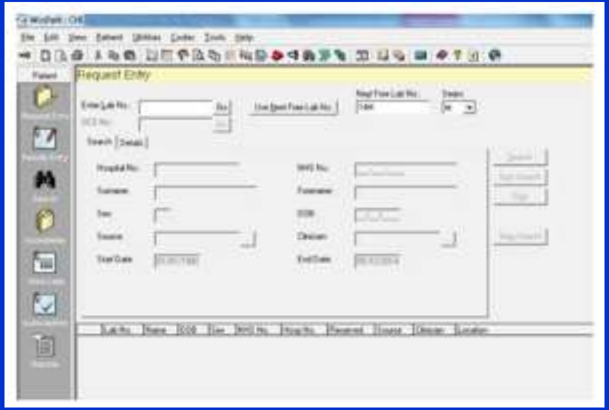
* AI suddenly attracted a lot of attention with the use of whole slide image technology; Digital Pathology (converting WSI to data and then analyse these data and link them to diagnosis, behaviour and response to therapy)

Pathology



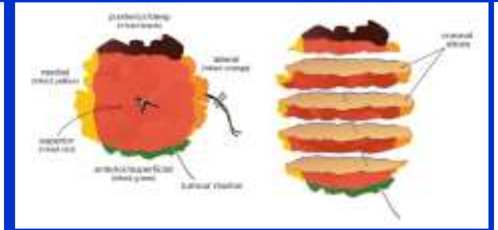


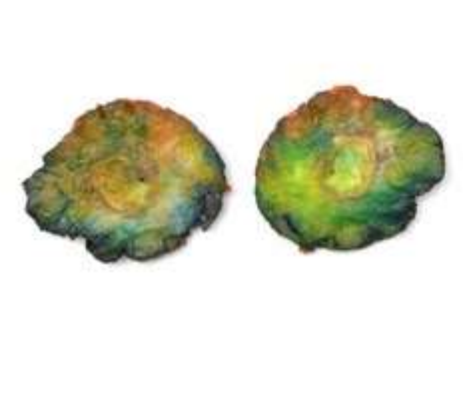
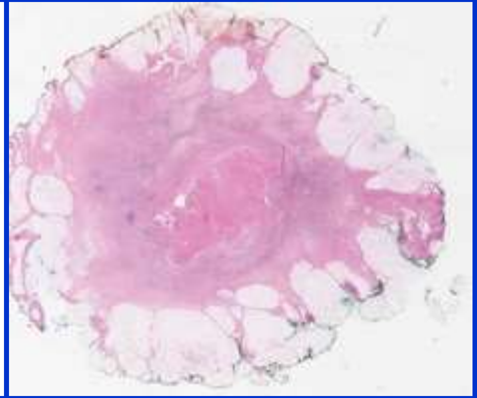



Request Entry


LABORATORY MEDICINE PROGRAM
Surgical Pathology Consultation Report

Pathology



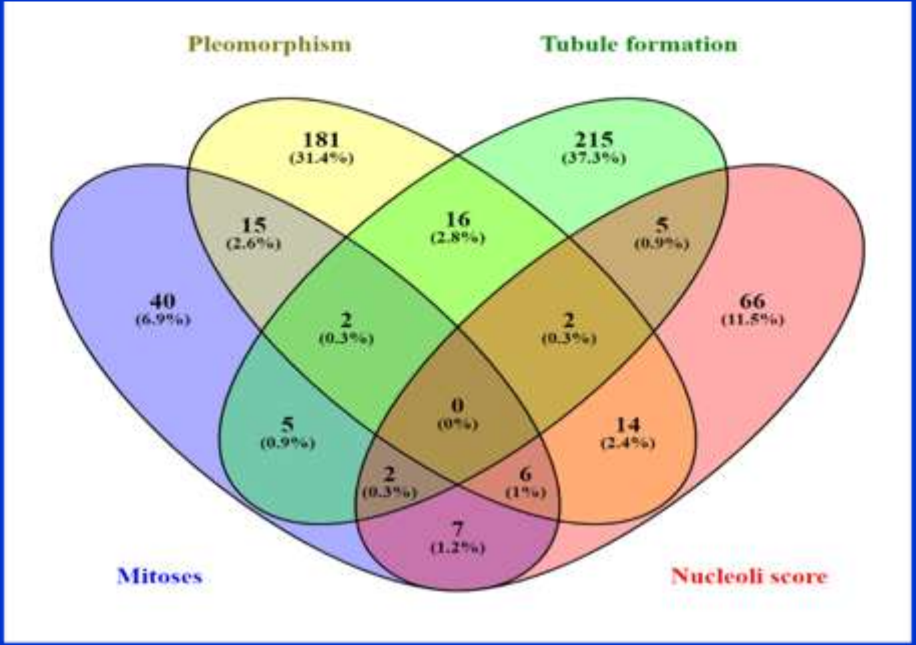
AI applications to WSI, outputs is back to the pathologist and integrated into the report

SWI-based AI algorithms

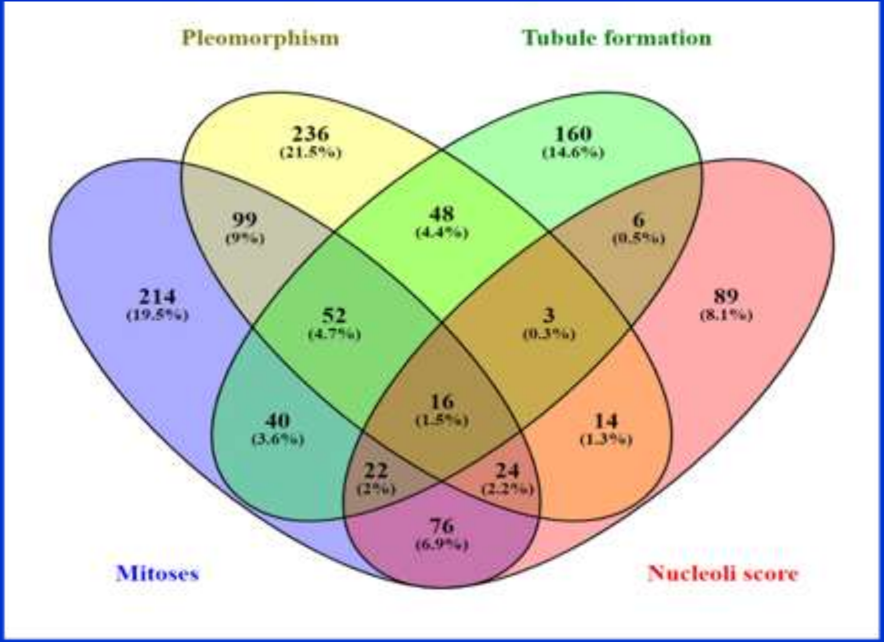
Molecular make up of tumours → Morphology of tumour tissue
Myriad of features on the slides (WSI)

AI →

- Improve workflow and system efficiency
- Refine classification
- Prediction of outcome:
  Lesions' behaviour & response to therapy



Down regulated genes



Up regulated genes

Histopathology

Article Open Access

Visual histological assessment of morphological features reflects the underlying molecular profile in invasive breast cancer: a morphomolecular study

Emad A Rakha, Mansour Alsaleem, Khloud A ElSharawy, Michael S Toss, Sara Raafat, Raluca Mihai, Fayyaz A Minhas, Andrew R Green, Nasir M Rajpoot, Leslie W Dalton, Nigel P Mongan ... See fewer authors

Deep learning model for the prediction of microsatellite instability in colorectal **cancer**: a diagnostic study.

Yamashita R, Long J, Longacre T, Peng L, Berry G, Martin B, Higgins J, Rubin DL, Shen J.

Lancet Oncol. 2021 Jan;22(1):132-141. doi: 10.1016/S1470-2045(20)30535-0.

Machine Learning Techniques for Classifying the Mutagenic Origins of Point Mutations

Yicheng Zhu, Cheng Soon Ong and Gavin A. Huttley

GENETICS *May 1, 2020 vol. 215 no. 1 25-40; https://doi.org/10.1534/genetics.120.303093*

Artificial Intelligence-based Detection of FGFR3 **Mutational** Status Directly from Routine Histology in Bladder Cancer: A Possible Preselection for Molecular Testing?

Loeffler CML, Ortiz Bruechle N, Jung M, Seillier L, Rose M, Laleh NG, Knuechel R, Brinker TJ, Trautwein C, Gaisa NT, Kather JN.

Eur Urol Focus. 2021 Apr 21:S2405-4569(21)00113-9. doi: 10.1016/j.euf.2021.04.007. Online ahead of print.

Artificial intelligence in clinical and genomic diagnostics

Raquel Dias & Ali Torkamani

Genome Medicine **11**, Article number: 70 (2019) | Cite this article

Histopathological characteristics and **artificial intelligence** for predicting tumor **mutational** burden-high colorectal cancer.

Shimada Y, Okuda S, Watanabe Y, Tajima Y, Nagahashi M, Ichikawa H, Nakano M, Sakata J, Takii Y, Kawasaki T, Homma KI, Kamori T, Oki E, Ling Y, Takeuchi S, Wakai T.

J Gastroenterol. 2021 Apr 28. doi: 10.1007/s00535-021-01789-w. Online ahead of print.

Journal of Pathology Informatics
Wolters Kluwer -- Medknow Publications

Deep Learning to Estimate Human Epidermal Growth Factor Receptor 2 Status from Hematoxylin and Eosin-Stained Breast Tissue Images

Deepak Anand, Nikhil Cherian Kurian, [...], and Amit Sethi

nature COMMUNICATIONS

ARTICLE
https://doi.org/10.1038/s41467-020-19334-3 OPEN
Check for updates

Deep learning-enabled breast cancer hormonal receptor status determination from base-level H&E stains

Nikhil Naik[1✉], Ali Madani[1,4], Andre Esteva[1,4], Nitish Shirish Keskar[1], Michael F. Press[2], Daniel Ruderman[3], David B. Agus[3] & Richard Socher[1]

AI can determine molecular marker status including hormone receptors and HER2, directly from cellular morphology of H&E stained WSI with high precision

SCIENTIFIC REPORTS
natureresearch
Check for updates

Deep learned tissue "fingerprints" classify breast cancers by ER/PR/Her2 status from H&E images

Rishi R. Rawat[1], Itzel Ortega[1], Preeyam Roy[1], Fei Sha[2], Darryl Shibata[3], Daniel Ruderman[1✉] & David B. Agus[1]

Deep learning radiomics model based on breast ultrasound video to predict **HER2** expression **status**.

Quan MY, Huang YX, Wang CY, Zhang Q, Chang C, Zhou SC.

Front Endocrinol (Lausanne). 2023 Apr 18;14:1144812. doi: 10.3389/fendo.2023.1144812.

Automated Molecular Subtyping of Breast Carcinoma Using Deep Learning Techniques.

Niyas S, Bygari R, Naik R, Viswanath B, Ugwekar D, Mathew T, Kavya J, Kini JR, Rajan J.

IEEE J Transl Eng Health Med. 2023 Feb 6;11:161-169. doi: 10.1109/JTEHM.2023.3241613.

AI tools to improve grade assignment

Pantanowitz *et al. Diagnostic Pathology* (2020) 15:80
https://doi.org/10.1186/s13000-020-00995-z

Diagnostic Pathology

RESEARCH Open Access

Accuracy and efficiency of an artificial intelligence tool when counting breast mitoses

Liron Pantanowitz[1,2*], Douglas Hartman[1], Yan Qi[3], Eun Yoon Cho[4], Beomseok Suh[5], Kyunghyun Paeng[5], Rajiv Dhir[1], Pamela Michelow[2], Scott Hazelhurst[6], Sang Yong Song[4†] and Soo Youn Cho[4†]

EBioMedicine

Published by THE LANCET

Commentary

Artificial intelligence-directed prognostication of breast cancer

Regular Article

SAGE

Agreement in Histological Assessment of Mitotic Activity Between Microscopy and Digital Whole Slide Images Informs Conversion for Clinical Diagnosis

Bih-Rong Wei, PhD[1,2], Charles H. Halsey, DVM, PhD[1], Shelley B. Hoover, BS[1],

Histopathology

Original Article

Artificial intelligence grading of breast cancer: a promising method to refine prognostic classification for management precision

Khloud A Elsharawy, Thomas A Gerds, Emad A Rakha, Leslie W Dalton

Clinical trial | Published: 01 May 2021

Machine learning-based image analysis for accelerating the diagnosis of complicated preneoplastic and neoplastic ductal lesions in breast biopsy tissues

Shinya Sato, Satoshi Maki, Takashi Yamanaka, Daisuke Hoshino, Yukihide Ota, Emi Yoshioka, Kae Kawachi, Kota Washimi, Masaki Suzuki, Yoichiro Ohkubo, Tomoyuki Yokose, Toshinari Yamashita, Seiji Ohtori & Yohei Miyagi

Breast Cancer Research and Treatment (2021) | Cite this article

JAMA Netw Open. 2019 Aug; 2(8): e198777.
Published online 2019 Aug 9.
doi: 10.1001/jamanetworkopen.2019.8777
PMCID: PMC6692690
PMID: 31397859

Assessment of Machine Learning of Breast Pathology Structures for Automated Differentiation of Breast Cancer and High-Risk Proliferative Lesions

Ezgi Mercan, PhD,[1,2] Sachin Mehta, MTech,[3] Jamen Bartlett, MD,[4,5] Linda G. Shapiro, PhD,[6] Donald L. Weaver, MD,[7] and Joann G. Elmore, MD, MPH[8]

The AI-based image analysis provided the following area under the curve values (AUC): Normal lesion versus DCIS, 0.9902; Normal lesion versus CCL, 0.9786; and UDH versus DCIS, 1.000.

Using 240 samples, the findings suggest that machine learning methods are potentially suitable as diagnostic support systems in differentiating challenging preinvasive lesions of the breast.

Critical Reviews in Oncology / Hematology 178 (2022) 103777

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

Accuracy of artificial intelligence-assisted detection of Oral Squamous Cell Carcinoma: A systematic review and meta-analysis

Ibrahim Elmakaty, Mohamed Elmarasi, Ahmed Amarah, Ruba Abdo, Mohammed Imad Malki

Am J Clin Pathol. 2021 Mar 15;155(4):527-536. doi: 10.1093/ajcp/aqaa151.

Artificial Intelligence Improves the Accuracy in Histologic Classification of Breast Lesions

António Polónia[1,2], Sofia Campelos[1,2], Ana Ribeiro[3], Ierece Aymore[1,2], Daniel Pinto[4], Magdalena Biskup-Fruzynska[5], Ricardo Santana Veiga[6], Rita Canas-Marques[7], Guilherme Aresta[8,9], Teresa Araújo[8,9], Aurélio Campilho[8,9], Scotty Kwok[10], Paulo Aguiar[2,11], Catarina Eloy[1,2,12]

Evaluation of tumour infiltrating lymphocytes in luminal breast cancer using **artificial intelligence**.

Makhlouf S, Wahab N, Toss M, Ibrahim A, Lashen AG, Atallah NM, Ghannam S, Jahanifar M, Lu W, Graham S, Mongan NP, Bilal M, Bhalerao A, Snead D, Minhas F, Raza SEA, Rajpoot N, Rakha E.

Br J Cancer. 2023 Sep 30. doi: 10.1038/s41416-023-02451-3. Online ahead of print.

Deciphering the Morphology of Tumor-Stromal Features in Invasive Breast Cancer Using **Artificial Intelligence**.

Atallah NM, Wahab N, Toss MS, Makhlouf S, Ibrahim AY, Lashen AG, Ghannam S, Mongan NP, Jahanifar M, Graham S, Bilal M, Bhalerao A, Ahmed Raza SE, Snead D, Minhas F, Rajpoot N, Rakha E.

Mod Pathol. 2023 Jun 26;36(10):100254. doi: 10.1016/j.modpat.2023.100254. Online ahead of print.

Artificial intelligence grading of breast cancer: a promising method to refine prognostic classification for management precision.

Elsharawy KA, Gerds TA, Rakha EA, Dalton LW.

Histopathology. 2021 Aug;79(2):187-199. doi: 10.1111/his.14354. Epub 2021 May 6.

PMID: 33590486

Visual histological assessment of morphological features reflects the underlying molecular profile in invasive breast cancer: a morphomolecular study.

Rakha EA, Alsaleem M, ElSharawy KA, Toss MS, Raafat S, Mihai R, Minhas FA, Green AR, Rajpoot NM, Dalton LW, Mongan NP.

Histopathology. 2020 Oct;77(4):631-645. doi: 10.1111/his.14199. Epub 2020 Sep 1.

Klimov *et al. Breast Cancer Research* (2019) 21:83
https://doi.org/10.1186/s13058-019-1165-5

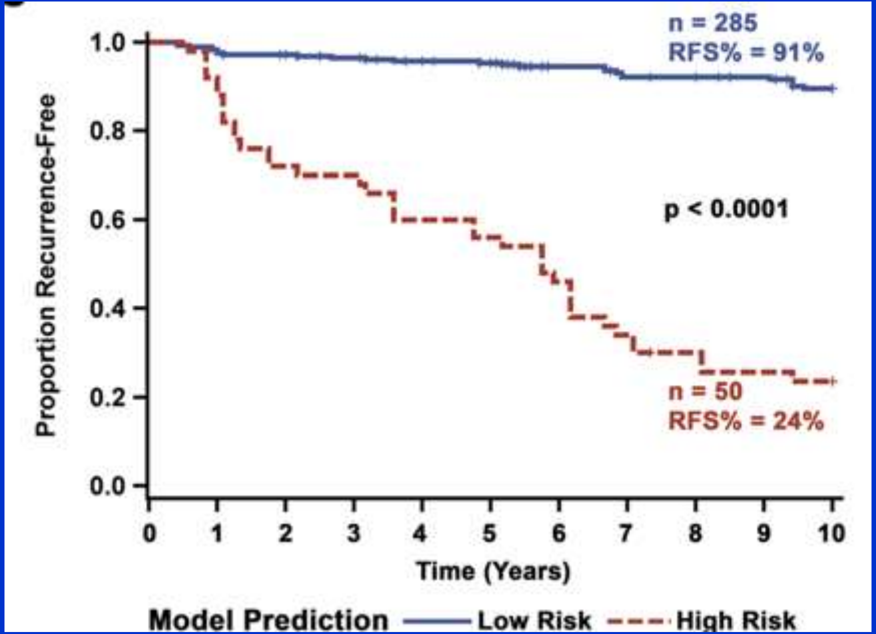
Breast Cancer Research

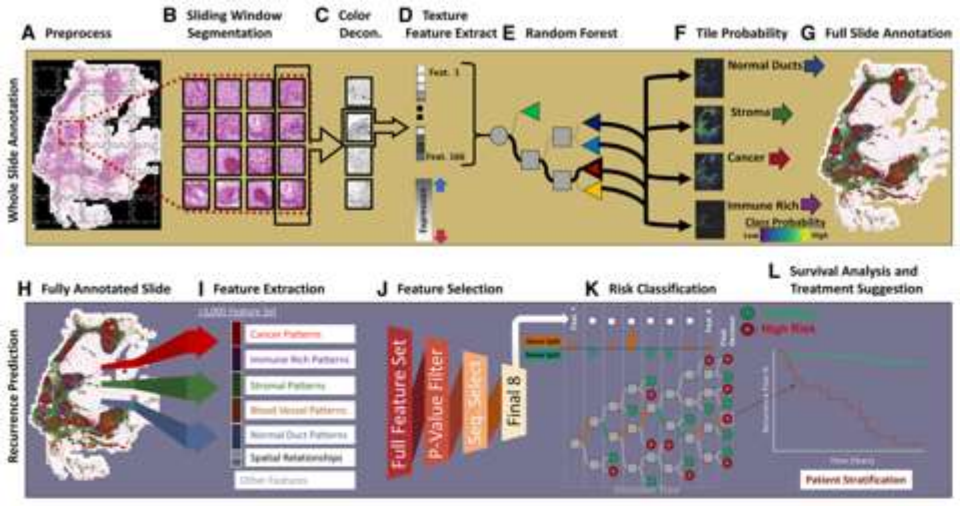
RESEARCH ARTICLE Open Access

A whole slide image-based machine learning approach to predict ductal carcinoma in situ (DCIS) recurrence risk

Check for updates

Sergey Klimov[1,4], Islam M. Miligy[2], Arkadiusz Gertych[3], Yi Jiang[4], Michael S. Toss[2], Padmashree Rida[1], Ian O. Ellis[2], Andrew Green[2], Uma Krishnamurti[5], Emad A. Rakha[2,6*] and Ritu Aneja[1*]





Predicting survival from colorectal cancer histology slides using deep learning: A retrospective multicenter study.

Kather JN, Krisam J, Charoentong P, Luedde T, Herpel E, Weis CA, Gaiser T, Marx A, Valous NA, Ferber D, Jansen L, Reyes-Aldasoro CC, Zörnig I, Jäger D, Brenner H, Chang-Claude J, Hoffmeister M, Halama N.

PLoS Med. 2019 Jan 24;16(1):e1002730. doi: 10.1371/journal.pmed.1002730. eCollection 2019 Jan.

Development of a Prognostic Algorithm for Breast Cancer (BRACE)

£14m grant to develop a reliable AI-based tool to predict the risk of distant metastasis and breast cancer (BC) related death in the indeterminate luminal BC risk group

npj | precision oncology   www.nature.com/npjprecisiononcology

ARTICLE OPEN

AI-enabled routine H&E image based prognostic marker for early-stage luminal breast cancer

Noorul Wahab, Michael Toss, Islam M. Miligy, Mostafa Jahanifar, Nehal M. Atallah, Wenqi Lu, Simon Graham, Mohsin Bilal, Abhir Bhalerao, Ayat G. Lashen, Shorouk Makhlouf, Asmaa Y. Ibrahim, David Snead, Fayyaz Minhas, Shan E. Ahmed Raza, Emad Rakha and Nasir Rajpoot

UK Research and Innovation

PathLAKE

University of Nottingham
UK | CHINA | MALAYSIA

Study Cohort

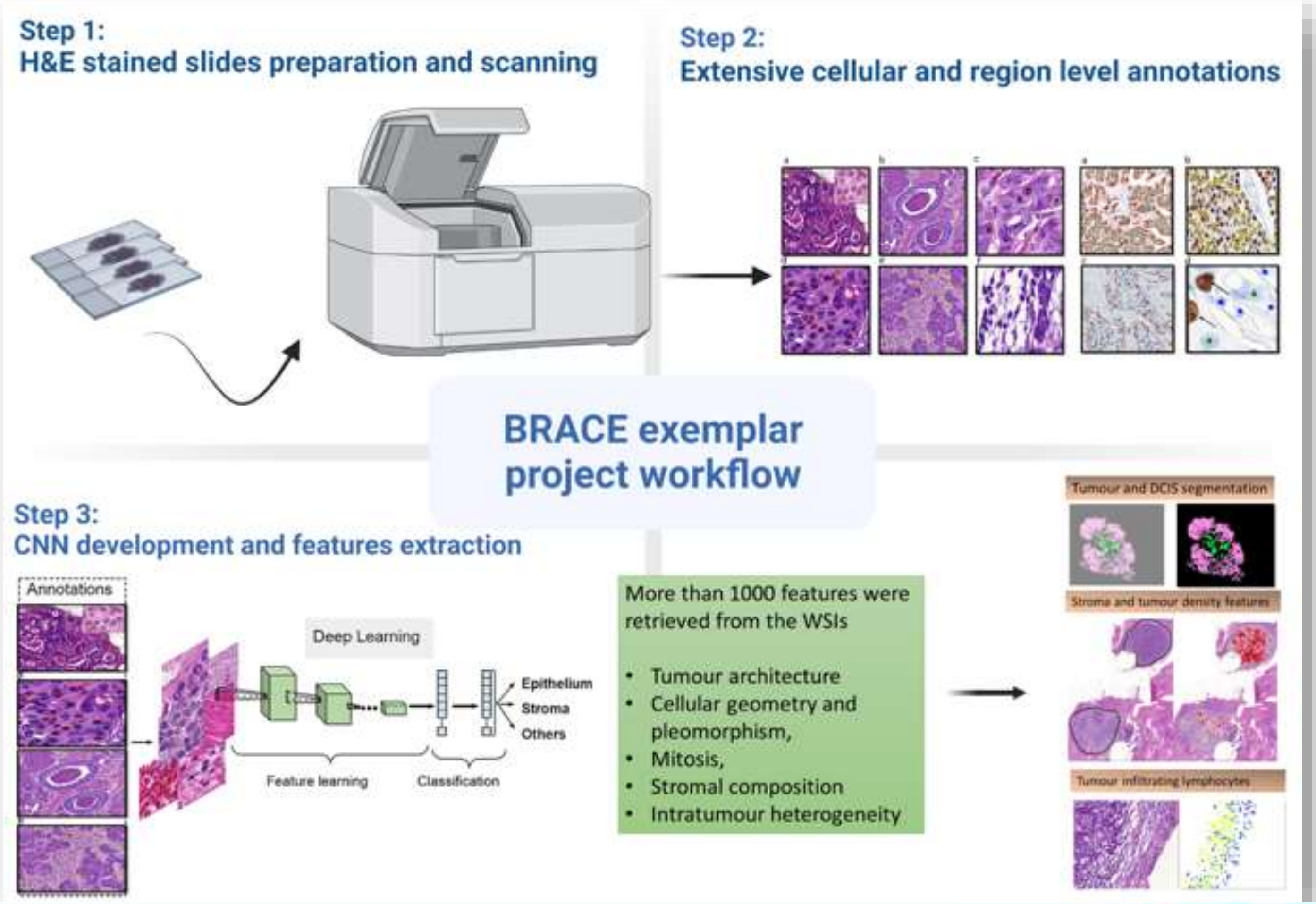
A large cohort (n=2,400) was selected from a cohort of 9,500 BC cases.

Inclusion Criteria

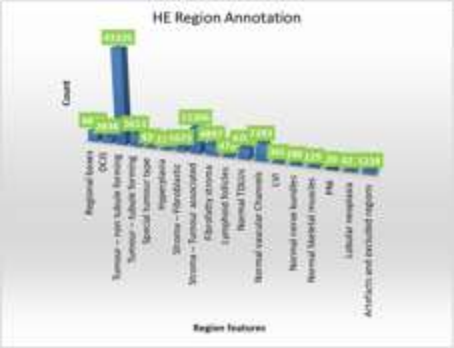
- ER+ HER2- LN negative & LN + (1-3)
- Hormone therapy
- Detailed clinic-pathological parameters
- Long term follow up data (10 years DMFS and 10 and 15 years BCSS)

Exclusion Criteria

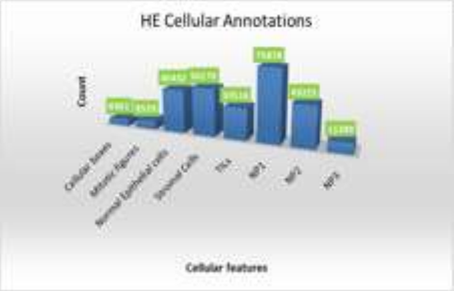
- Neoadjuvant therapy,
- Advanced /metastatic BC
- HER2+, TNBC, patients
- Stage 3 LN (>3 positive nodes)
- chemotherapy (or any other systemic therapy)



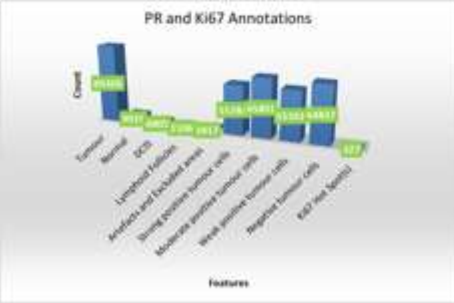
Step 1:
H&E stained slides preparation and scanning
Step 2:
Extensive cellular and region level annotations
BRACE exemplar
project workflow
Step 3:
CNN development and features extraction
Annotations
Deep Learning
Epithelium
Stroma
Others
Feature learning
Classification
More than 1000 features were retrieved from the WSIs
• Tumour architecture
• Cellular geometry and pleomorphism,
• Mitosis,
• Stromal composition
• Intratumour heterogeneity
Tumour and DCIS segmentation
Stroma and tumour density features
Tumour infiltrating lymphocytes



HE Region Annotation
Count
Region features



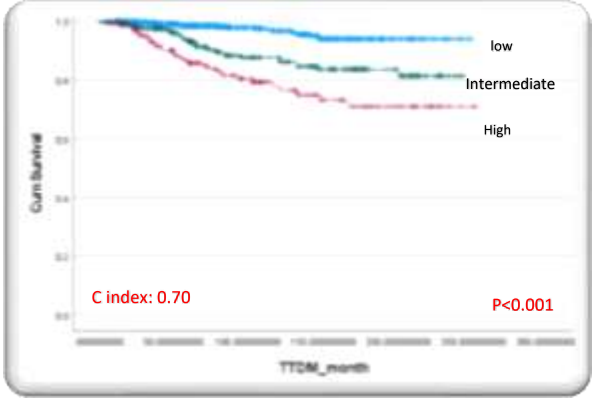
HE Cellular Annotations
Count
Cellular features



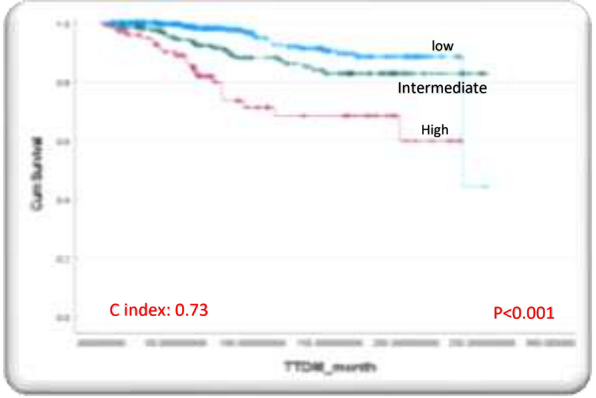
PR and Ki67 Annotations
Count
Features

Results and outcomes

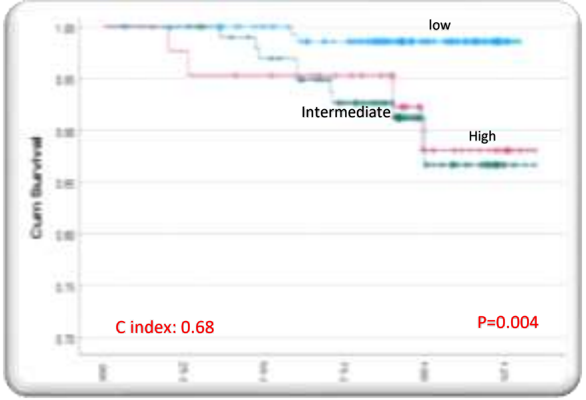
Discovery Set



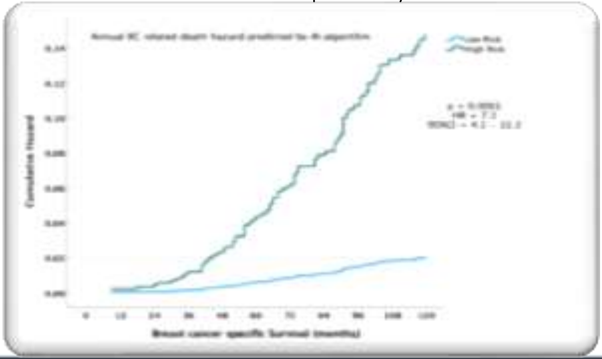
Internal test set



External test set



Annual BC related death hazards predicted by the AI risk score

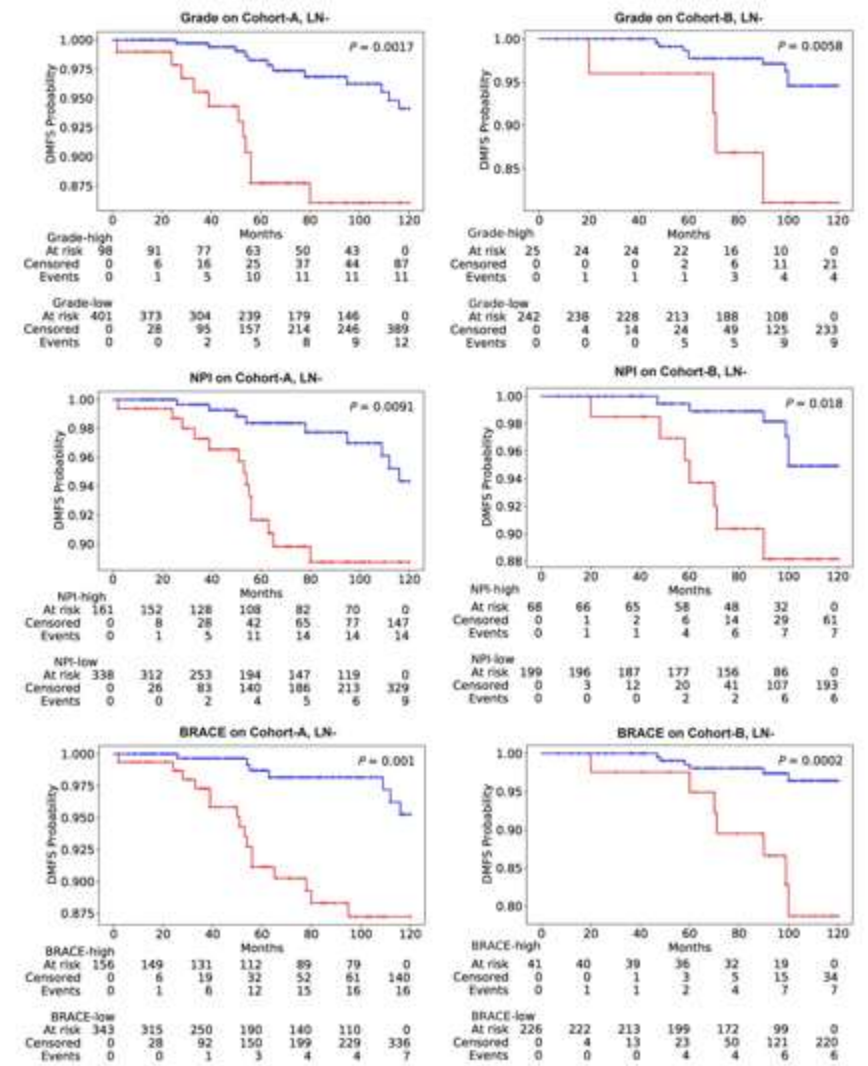


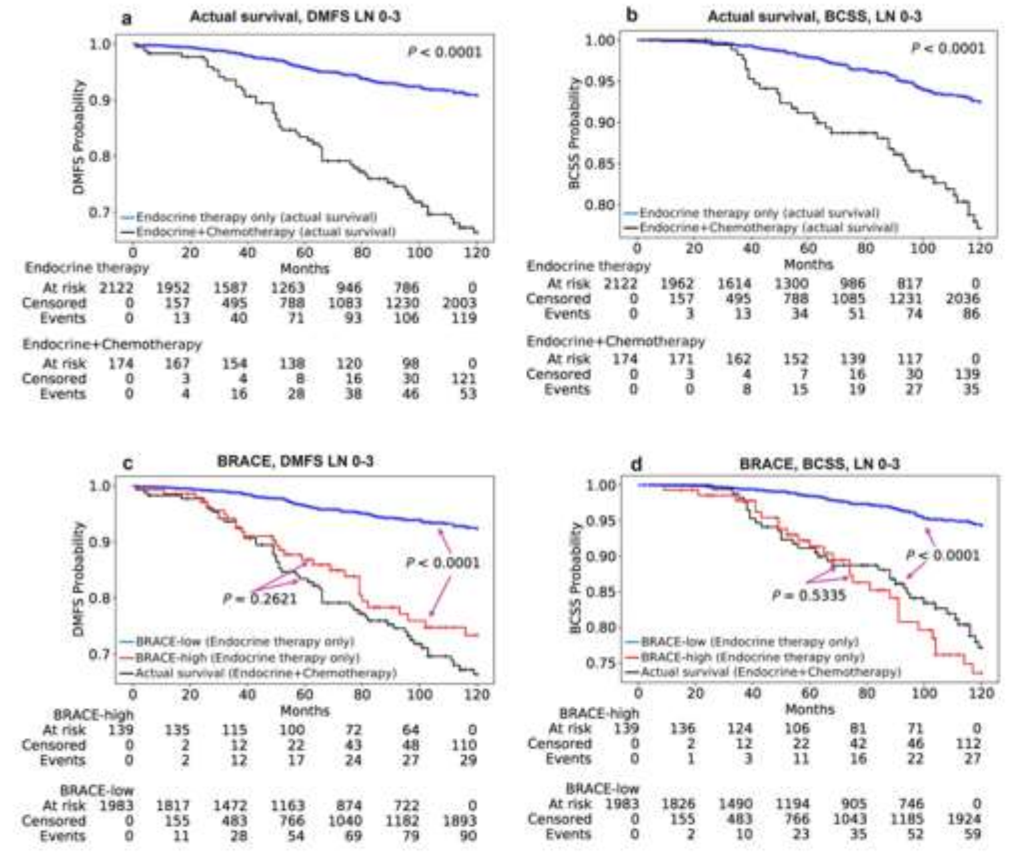
Multivariate cox regression analysis

Variables	Hazard Ratio	95% CI	P value
Low AI risk score Intermediate AI risk score High AI risk score	1 2.2 3.2	 1.5 - 3.3 1.9 - 5.1	**<0.001**
Grade 1 Grade 2 Grade 3	1 1.5 2.3	 0.8 - 2.8 1.2 - 4.46	**0.02**
Lymphvascular invasion	1.8	1.3 - 2.7	**0.001**
Lymph node metastasis	1.9	1.4 - 2.7	**<0.001**
Tumour size	1.1	0.9 - 1.3	0.3

High correlation with Oncotype Dx data with high sensitivity and specificity

Oncotype DX score / AI based score	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
	80%	80%	67%	89%	81%





npj | precision oncology www.nature.com/npjprecisiononcology

ARTICLE OPEN

AI-enabled routine H&E image based prognostic marker for early-stage luminal breast cancer

Pathology: Applications

1-Streamline of the workflow

2-Diagnostic applications

3-Prognosis and prediction

4-Other applications:

Precision medicine

Contents lists available at ScienceDirect
The Breast
journal homepage: www.elsevier.com/brst

Original article

Artificial intelligence in digital breast pathology: Techniques and applications

Asmaa Ibrahim[a,1], Paul Gamble[b,1], Ronnachai Jaroensri[b,1], Mohammed M. Abdelsamea[c], Craig H. Mermel[b], Po-Hsuan Cameron Chen[b], Emad A. Rakha[a,*]

J Clin Pathol 2020;**0**:1–6. doi:10.1136/jclinpath-2020-206908

Review

Current and future applications of artificial intelligence in pathology: a clinical perspective

Emad A Rakha,[1] Michael Toss,[1] Sho Shiino,[1] Paul Gamble,[2] Ronnachai Jaroensri,[2] Craig H Mermel,[2] Po-Hsuan Cameron Chen[2]

Digital Technology in Diagnostic Breast Pathology and Immunohistochemistry.

Rakha EA, Vougas K, Tan PH.

Pathobiology. 2022;89(5):334-342. doi: 10.1159/000521149. Epub 2021 Dec 30.

AI in (Breast) Pathology: Applications

Streamline of the workflow

- Can help in distribution and prioritisation of cases

- Automatic QC of cases (stain quality and tissue representations)

- Tumour detection AI: Automatic request of extra-tests in time (before reporting), e.g., ER, PR and HER2, +/- PDL1, Ki67 and E-cadherin

- Automatic coding of biopsies (B1 to B5) / provide initial diagnosis

- Automatic quantification of IHC markers, TILs and histological grade

Automated quality assessment of large digitised histology cohorts by **artificial intelligence**.
Haghighat M, Browning L, Sirinukunwattana K, Malacrino S, Khalid Alham N, Colling R, Cui Y, Rakha E, Hamdy FC, Verrill C, Rittscher J.
Sci Rep. 2022 Mar 23;12(1):5002. doi: 10.1038/s41598-022-08351-5.

AI in Pathology: Applications

Diagnostic applications:

- Report normal cases such as prophylactic mastectomies, reductions specimens and re-excision specimens

- Report of lymph nodes (highlight suspicious nodes for review)

- Primary or secondary reporting of certain lesions such fibroadenoma, papilloma, RS/CSL, tumour grade, type….etc (at least as "*second opinion*")

- Reduce time of reporting by heightening certain features such as vascular invasion, and distance to margins

- Provide an automated report allowing that time to be spent on more important cases

AI in Pathology: Applications

Improve quality and accuracy of pathology diagnosis

- In challenging cases: provide list of differential diagnosis, suggest further tests and reported subjectivity of such a diagnosis and the reported need of second opinion

- Provide "second opinion" diagnosis to improve accuracy (Diagnostic WSI banks)

- Improve diagnostic QA in pathology by diagnostic audits and secondary reporting

- Decision support tools in histopathology

AI in Pathology: Applications

Prognostic and Predictive Applications

- Objective assessment of prognostic morphological features such as grade

- Identify myriads of tumour morphological features and link them to outcome and response to therapy to provide cost-efficient image-based prognostic and predictive assays

- Identify and translate tumour morphological features linked to underlying molecular features to provide surrogate assays to the expensive multigene tests

AI in Breast Pathology: Applications

Prognostic and Predictive Applications

* AI can link
- image-based data of primary tumour morphological features such as tumour type, grade, architecture, and size and tumour microenvironment

- Receptors, and IHC data

- Possibility Omics and imaging data if available to provide more comprehensive model for an accurate prediction of outcome and response to therapy

* Identify high risk patients for monitoring and for further genetic testing

AI in Breast Pathology: Challenges

* Performance of AI algorithms in clinical setting (quality measures, degree of validation, performance in rare and complex cases): *Actual Clinical Utility*

* Scientific and regulatory issues & Level of adoption of DP in the clinical setting

* Integration of AI algorithms in the routine reporting workflow

* User satisfaction (pathologists' perception, confidence, real-time saving)

* Costs-benefits of AI algorithms and added value to patients, NHS and pathologists

Will there still be a need for breast pathologists in the future?

AI will not replace the expertise and experience of pathologists, rather

- provide data and insights beyond traditional microscopy, or DP only
- facilitate the work of the pathologist by automation and algorithms
- Save pathologists' time to focus on challenging cases
- Can provide prognostic and predictive information to replace expensive multigene tests
- Improve accuracy and precision pathology (secondary diagnosis, double reporting, audits…etc)

AI and computational pathology will assist rather than replace the pathologist

Any questions?