Computational pathology

Ian Cree

Honorary Professor of Pathology,
Institute of Ophthalmology,
University College London, UK

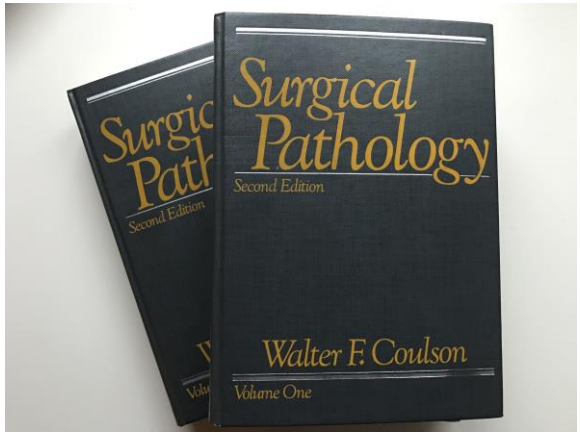
Declaration of Interests

- Honorary Honorary Professor of Pathology, Institute of Ophthalmology, University College London, UK
- Director, CanTech Ltd, Northamptonshire, UK
- Former Head of the WHO Classification of Tumours Programme and the Section of Evidence Synthesis and Classification at the International Agency for Research on Cancer, part of the World Health Organisation, Lyon, France.
- Previously implemented the GE Omnyx digital pathology system for reporting histopathology in Coventry, UK

- All opinions expressed are personal, and not those of any of the organisations above.

Pathology in the past…

- A microscope
- A good library – two volumes should do it…
- What's this ridiculous idea about antibodies?
- Electron microscopy?



Pathology today

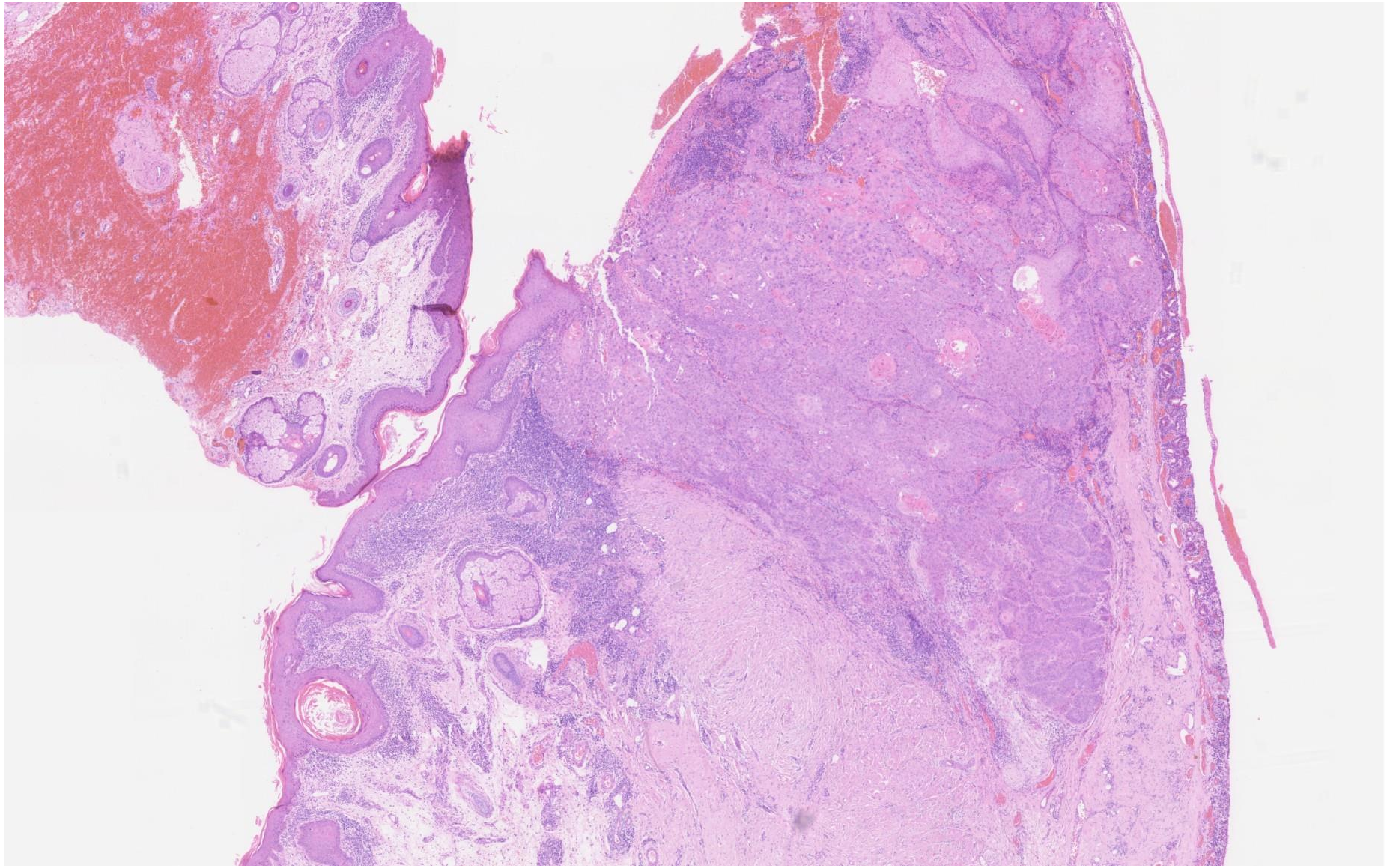
- Microscope
- Dusty bookshelves full of out of date texts (I bought the last one, and the diagnoses haven't changed much…)
- Internet if you're stuck?
- Immunohistochemistry works well...does anyone use electron microscopy anymore?
- Better send off a few sections for molecular pathology – I wonder what they do all day?

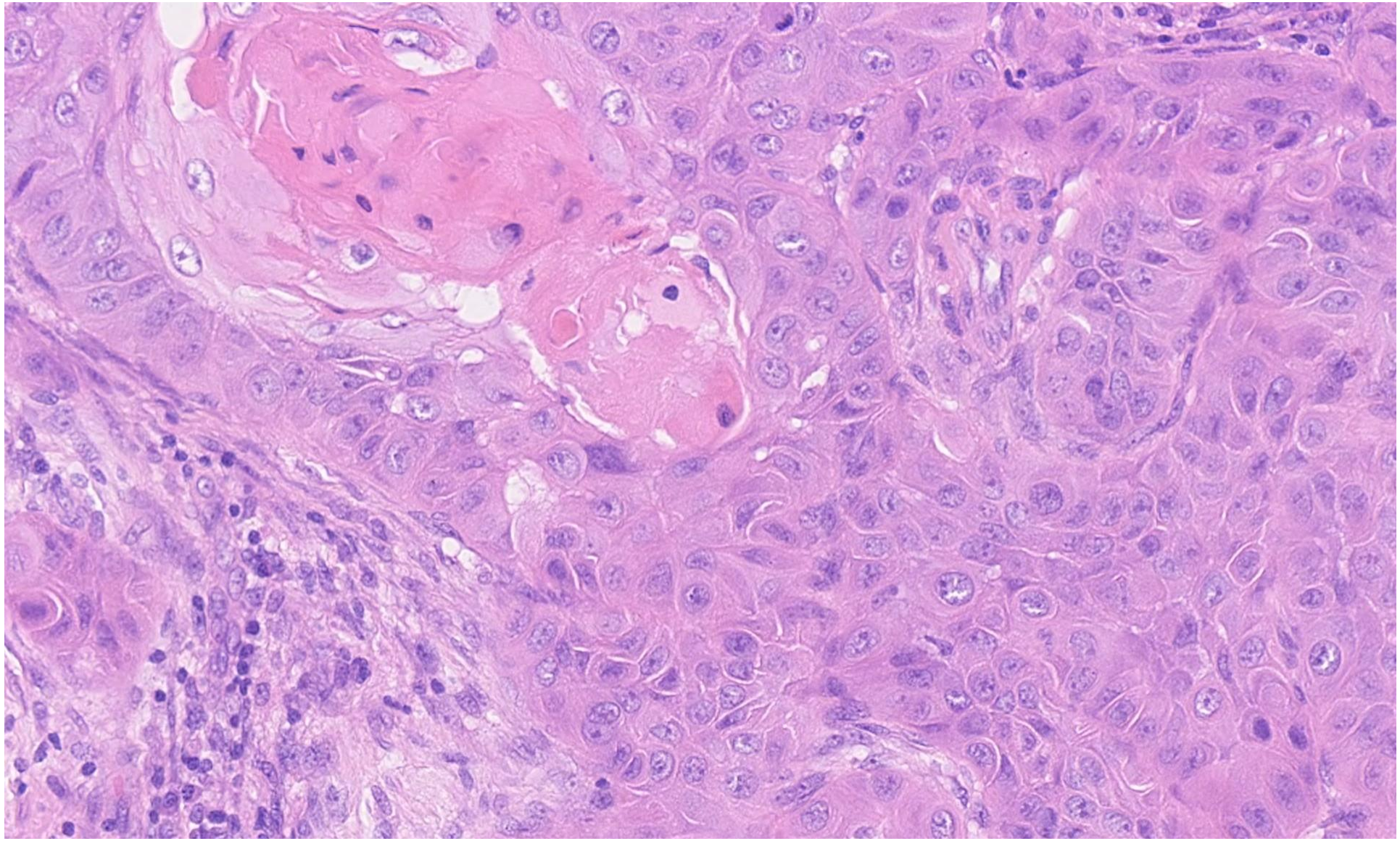
Pathology of the Future?

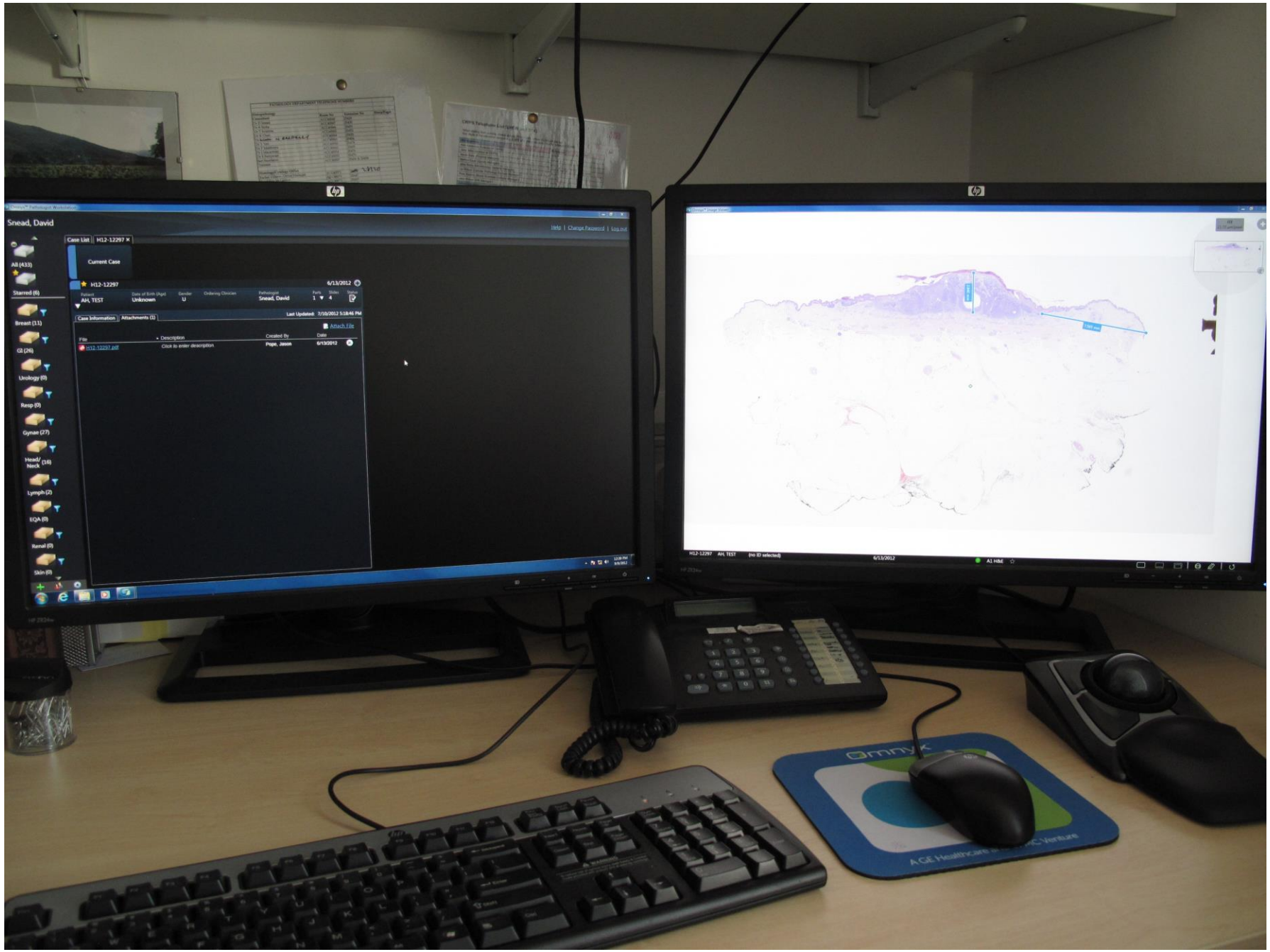
- Digital pathology with computer assisted (AI) diagnosis.
- Immunohistochemistry and image analysis.
- Next-generation sequencing of panels of gene, exome or WGS (complementary diagnostics).
- Proteins, RNA, Metabolome.
- Integrated reporting – LIMS or EPR?
- Diagnosis and predictive measurements to underpin treatment.
- Continuous education…books?

Intuitive, Easy To Use, Automatic


No Case Selected
Leica





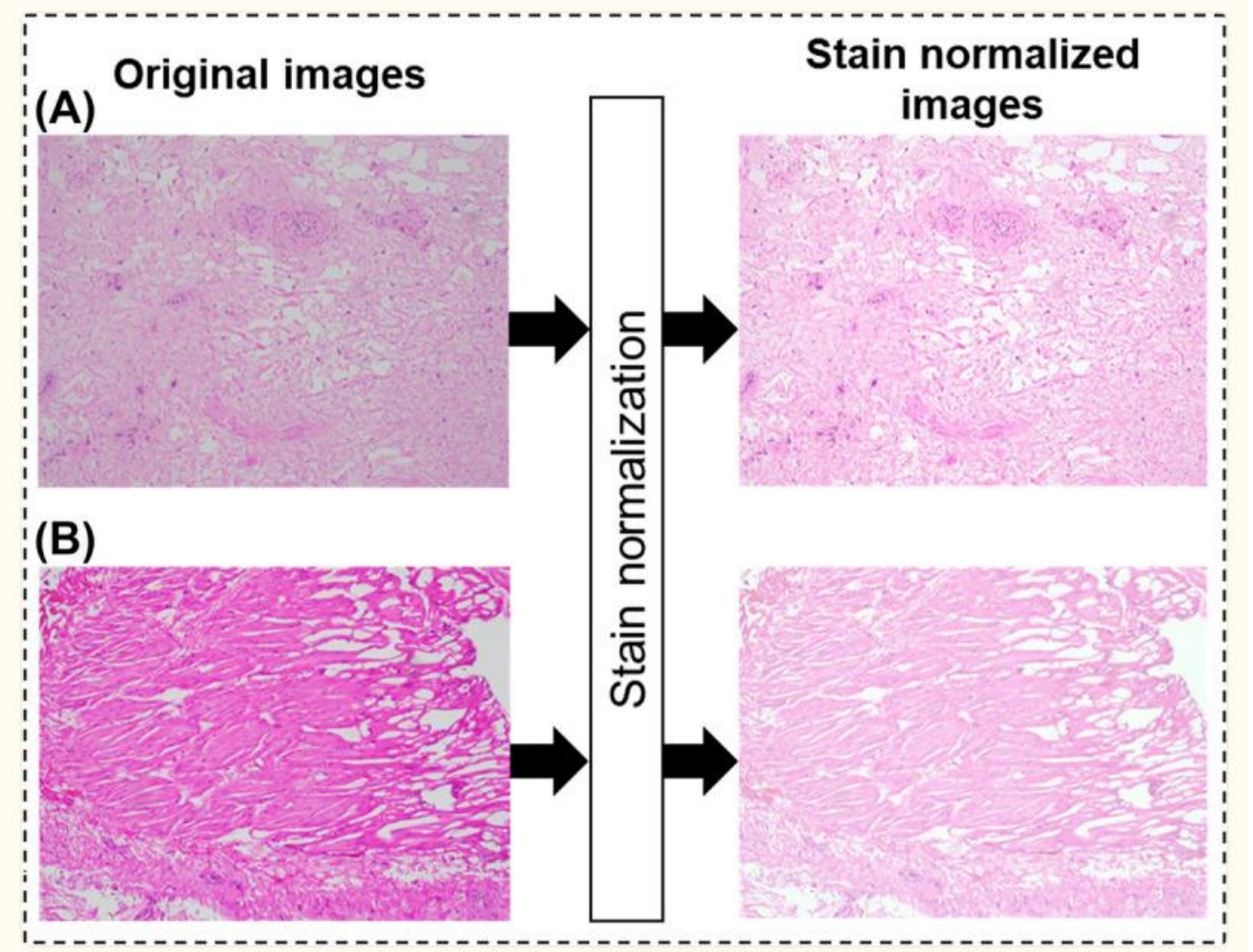

Snead, David
Case List
H12-12297
Current Case
Case Information
Attachments (1)
Omnyx

Validation study

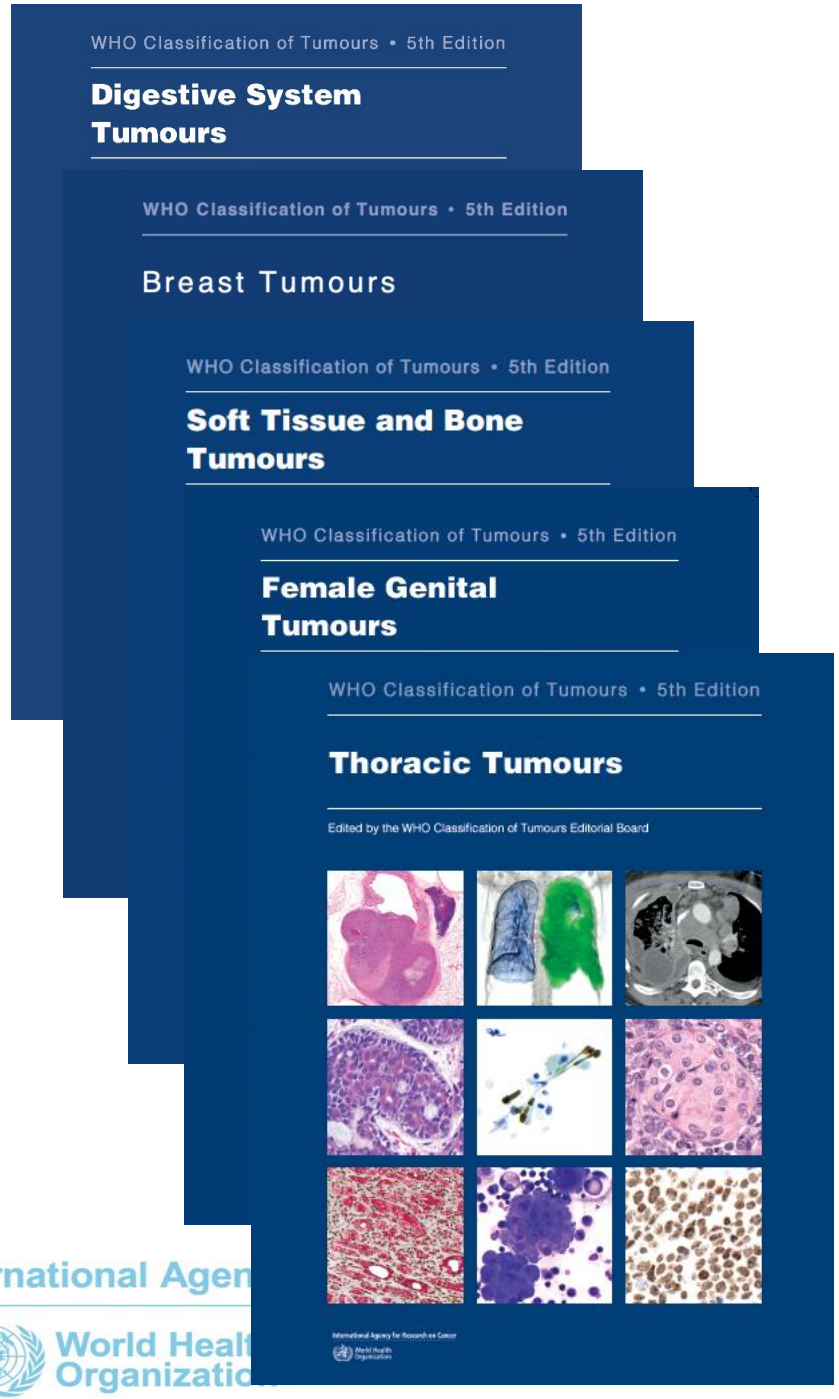
- Double reporting by same pathologist
- Glass first digital second
- Minimum 3 week ‘washout’ period
- 3,034 cases - 10,138 scanned slides (2.22 terabytes) giving 80% power at $\alpha = 0.05$
- Omnyx funded
- Results showed <2.4% discrepancies (72)

Snead DR *et al.* Validation of digital pathology imaging for primary histopathological diagnosis. *Histopathology* 2015 Sep 26. doi: 10.1111/his.12879.

Stain normalisation



Subramanya SK, Li R, Wang Y, Miyamoto H, Cui F. Deep learning for histopathological segmentation of smooth muscle in the urinary bladder. BMC Med Inform Decis Mak. 2023 Jul 15;23(1):122. PMID: 37454065



WHO Classification of Tumours

2.0: Tumours of the oesophagus: Introduction

Lam AK
Ochiai A
Odze R

This chapter describes benign and malignant oesophageal tumours of epithelial differentiation and
The ICD-O-4 topographical coding for t
ered in this chapter is presented in Box
common benign lesion, squamous pap
a dedicated section. Throughout this fi
precursor lesions are typically describ
from malignant tumours – a change fro
decision to make this change was bas
expansion of our understanding of the b
cal features of precursor lesions and th
practice.
There are two main types of precursor
gus: Barrett dysplasia and squamous d
10 years or so, we have seen an impo
towards ablation for the treatment of
patients with high-grade dysplasia. The
ally occur in the treatment of low-grad

Box 2.XX ICD-O-4 topographical coding for the anatomical sites covered in this chapter

Fig. 2.XX National age-standardized incidence rates cell carcinoma (SCC).

2.1.2.2: Oesophageal squamous dysplasia

Takubo KT
Fujii SF

Definition
Squamous dysplasia of the oesophagus is an unequivocal neoplastic alteration of the oesophageal squamous epithelium, without invasion.

ICD-O coding
80770/0 Low-grade squamous dysplasia
80770/2 High-grade squamous dysplasia

ICD-11 coding
2E92.0 & XH3Y37 Benign neoplasm of oesophagus & Oesophageal squamous intraepithelial neoplasia (dysplasia), low-grade
2E60.1 & XH9ND8 Carcinoma in situ of oesophagus & Oesophageal squamous intraepithelial neoplasia (dysplasia), high-grade

Related terminology
None

Subtype(s)
None

Localization
Squamous dysplasia can occur anywhere in the oesophagus, and it is likely to follow the distribution of squamous cell carcinoma.

Clinical features
Patients at high risk of oesophageal squamous cell carcinoma are usually followed using a combination of Lugol's chromoendoscopy and narrow-band imaging [1366]. With Lugol's iodine, low-grade dysplasia appears as an unstained or weakly stained area; high-grade dysplasia is consistently unstained [2974]. Features associated with neoplastic disease include large size, non-flat appearance, positive pink-colour sign, and multiplicity of distinct iodine-unstained lesions [3702]. On narrow-band imaging, dysplastic lesions appear as areas of brownish discolouration [2250,2202]. Abnormalities on narrow-band imaging reflect the invasion depth of intramucosal carcinoma and changes of intrapapillary capillary loops [2458].

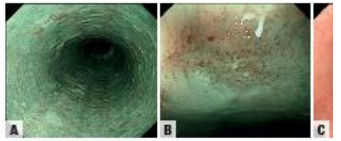


Fig. 2.XX Oesophageal squamous dysplasia. A On low-magnification endoscopy with narro the front left wall, 30 cm from the incisor. B On high-magnification endoscopy with narrow-ba between them is brightly coloured. C On white-light endoscopy, the lesion appears as a flat, lesion is positive for the pink-colour sign – it is well demarcated and unstained.

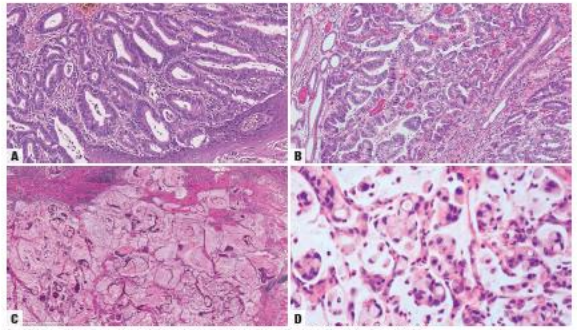


Fig. 2.XX Oesophageal adenocarcinoma. A Tubular pattern. B Papillary pattern. C Mucinous pattern. D Signet-ring cell pattern.

In recent years, next-generation sequencing techniques have given rise to global projects involving whole-genome sequencing of oesophageal adenocarcinoma [2566]. These projects have revealed key gene pathways and mutations involved in pathogenesis [2927,907], identified novel genes [818], and shown that the genomic landscapes of prechemotherapy and postchemotherapy samples of oesophageal adenocarcinoma are similar [2367]. There are currently no clinical applications for these comprehensive but complex data, but clinically relevant and diagnostically useful prognostic and predictive markers may emerge in the future. Data from The Cancer Genome Atlas (TCGA) also suggest that oesophageal adenocarcinoma strongly resembles gastric carcinoma with chromosomal instability [2602].

Macroscopic appearance
Oesophageal adenocarcinomas often present in advanced stages and appear as stricturing, polypoid, fungating, ulcerative, or diffuse infiltrating lesions. In earlier stages, adenocarcinomas may appear as irregular plaques. Early-stage carcinomas may present as small nodules or may not be detected on endoscopy. Adjacent to the carcinoma, there may be irregular tongues of reddish mucosa (resembling a salmon patch) that represent Barrett oesophagus and reflux changes and that contrast with the greyish-white colour of the squamous-lined oesophageal mucosa.

Histopathology
Oesophageal adenocarcinoma shows gastric, intestinal, and mixed (hybrid) lineage, evidenced by a combination of morphological and immunohistochemical features [1548,426].

The mucosa adjacent to the adenocarcinoma may show Barrett dysplasia and intestinal metaplasia (Barrett oesophagus). Oesophageal adenocarcinomas can be classified as having tubular, papillary, mucinous, and signet-ring cell patterns. Only limited evidence of the relevance of these patterns is available; therefore, patterns are described rather than subtypes. A mixture of these patterns is often seen. The tubular pattern is most common. It is characterized by irregular, single or anastomosing tubular glandular structures lined by a layer of single or stratified malignant epithelium; neoplastic glands often show variable amounts of intracellular mucin production and may show dilatation [1756]. The papillary pattern is characterized by papillae, with rare cases showing micropapillary architecture [1182]. The mucinous pattern generally shows carcinoma cells floating in

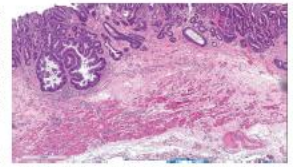


Fig. 2.XX Oesophageal adenocarcinoma. An example in Barrett oesophagus with a double layer of muscularis mucosae.

Add Personal Note

Send Feedback

Authors

Responsible Editor
Paul J. van Diest

Responsible Author
Shabnam Jaffer

Co-Author
Leonard Silva
Suzuko Moritani

Ductal adenoma

Definition
Ductal adenoma is a benign tumour composed of distorted glands in a sclerotic stroma surrounded by a fibrous capsule.

ICD-O coding
8503/0 Duct adenoma NOS

ICD-11 coding
2F30.2 & XH4LZ4 Intraductal papilloma of breast & Intraductal papilloma

Related terminology
Not recommended: sclerosing papilloma.

Subtype(s)
None

Localization
Ductal adenoma arises in medium-sized and small ducts of the peripheral breast.

Clinical features
Ductal adenoma usually presents as a palpable solitary lump, but it may have an irregular appearance when multifocal. It usually arises from the small and medium-sized ducts. Rarely, it can involve the larger ducts and present with nipple discharge, similar to intraductal papilloma. Mammography shows a discrete mass, poorly defined margins, spiculation, multilobulation, and/or irregularly shaped calcifications. Sonography shows a well-defined, round hypoechoic nodule, with shadowing and posterior enhancement. Few cases of infarction have been described in pregnancy and lactation { 17146162 }.

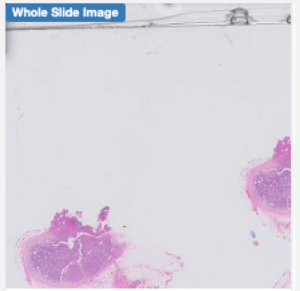
Epidemiology
Ductal adenoma is a rare tumour that occurs in the sixth decade of life. It has been described in four cases to be bilateral and associated with Carney complex { 8764753 }.

Etiology
Ductal adenoma predominantly arises from the small and medium-sized ductal lumina in the peripheral breast, but it may rarely arise from the larger ducts { 2550351 }. In contrast, intraductal papilloma arises from both small to medium-sized peripheral ducts and predominantly larger subareolar ducts.

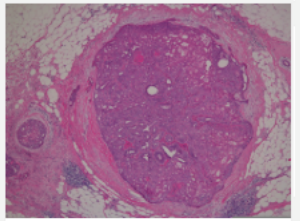
Pathogenesis
It is hypothesized that ductal adenoma most likely originates from intraductal papilloma in small and medium-sized ducts. Due to a stromal repair process, intraductal papilloma may undergo sclerosis, which is manifested by a myofibroblastic proliferation and deposition of fibronectin and interstitial collagen, resulting in loss of the arborizing papillary architecture. Overlapping features of radial scar (e.g. central elastosis) may also be seen, because radial scars in ductal adenoma are considered part of the spectrum of papillary lesions. Some authors contend that a hyperplastic process such as sclerosing adenosis, which is prevalent in ductal adenoma, may lead to ductal adenoma by direct expansion into small and medium-sized ducts or into a coexistent intraductal papilloma. The few cases of ductal adenoma that have been studied using next-generation sequencing show mutations in *PIK3CA*, *GNAS*, and *AKT1* { 27438523 }. *AKT1* mutations have also been detected in intraductal papillomas { 19898424 }, supporting a close relationship with (or an origin similar to that of) ductal adenomas.

Macroscopic appearance
Ductal adenomas range in size from 0.5 to 5.0 cm (average: 0.85 cm) and present as a discrete, white, solid nodule. On cut surface, they are lobulated and granular, with central grey softening. Calcified areas may seem firm, gritty, and pseudoinvasive. Focal attachment to a dilated cyst or duct may occasionally be seen. Rarely, the tumour may have a poorly defined edge that is firmly adherent to the surrounding breast stroma, raising suspicion for an invasive carcinoma. Additionally, ductal adenoma can be multinodular due to involvement of proximal or distal parts of the same ductal system.

Histopathology
Ductal adenoma is usually a solitary solid adenomatous proliferation surrounded by a densely thickened concentric fibroelastotic wall, but it may be multinodular at times. The



#7614


#1854
Ductal adenoma

tumourclassification.iarc.who.int

BlueBooksOnline

International Agency for Research on Cancer
World Health Organization

WHO Classification of Tumours

Breast tumours// Epithelial tu

AAA

Add Personal Note

Send Feedback

Authors

Responsible Editor
Paul J. van Diest

Responsible Author
Shabnam Jaffer

Co-Author
Leonard Silva
Suzuko Moritani

Ductal adenoma

Definition
Ductal adenoma is a benign tumour compose

ICD-O coding
8503/0 Duct adenoma NOS

ICD-11 coding
2F30.2 & XH4LZ4 Intraductal papilloma of bre

Related terminology
Not recommended: sclerosing papilloma.

Subtype(s)
None

Localization
Ductal adenoma arises in medium-sized and s

Clinical features
Ductal adenoma usually presents as a palpab the small and medium-sized ducts. Rarely, it can involve the larger ducts and present mass, poorly defined margins, spiculation, multilobulation, and/or irregularly shaped ca and posterior enhancement. Few cases of infarction have been described in pregnancy a

Epidemiology
Ductal adenoma is a rare tumour that occurs Carney complex { 8764753 }.

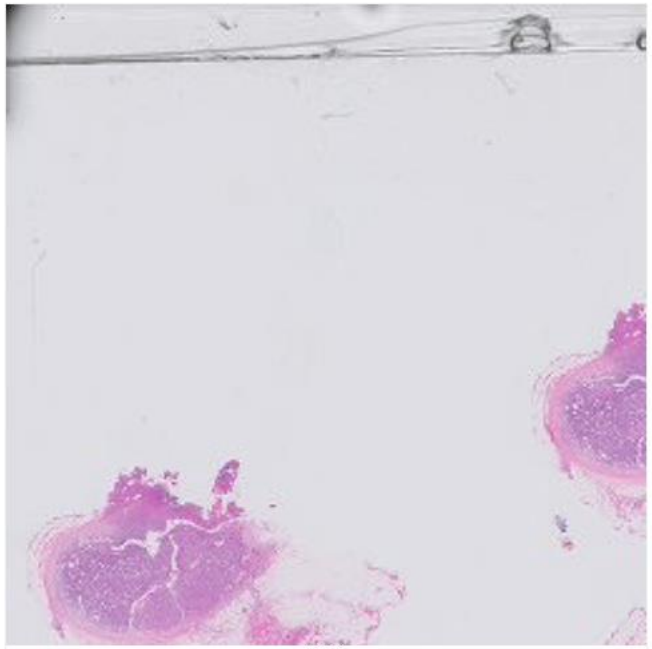
Etiology
Ductal adenoma predominantly arises from t m the larger ducts { 2550351 }. In contrast, intraductal papilloma arises from both small to

Pathogenesis
It is hypothesized that ductal adenoma most al repair process, intraductal papilloma may undergo sclerosis, which is manifested by a loss of the arborizing papillary architecture. Overlapping features of radial scar (e.g. cent of the spectrum of papillary lesions. Some authors contend that a hyperplastic process denoma by direct expansion into small and medium-sized ducts or into a coexistent intra tion sequencing show mutations in *PIK3CA*, *GNAS*, and *AKT1* { 27438523 }. *AKT1* mutatio hip with (or an origin similar to that of) ductal adenomas.

Macroscopic appearance
Ductal adenomas range in size from 0.5 to 5.0 cm (average 0.80 cm) and present as a discrete, white, solid nodule. On cut surface, they are lobulated and granular, with central grey softening. Calcified areas may seem firm, gritty, and pseudoinvasive. Focal attachment to a dilated cyst or duct may occasionally be seen. Rarely, the tumour may have a poorly defined edge that is firmly adherent to the surrounding breast stroma, raising suspicion for an invasive carcinoma. Additionally, ductal adenoma can be multinodular due to involvement of proximal or distal parts of the same ductal system.

Histopathology
Ductal adenoma is usually a solitary solid adenomatous proliferation surrounded by a densely thickened concentric fibroelastotic wall, but it may be multinodular at times. The

Attachment



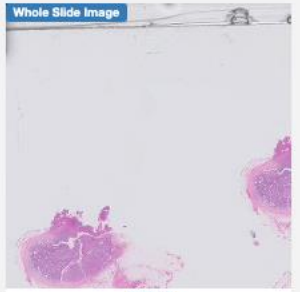
#7614

View WSI

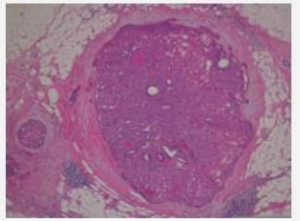
Diagnosis:
Legend:
Ductal adenoma consists of an encapsulated solid nodule of round and oval glands within fibrous stroma. Apocrine metaplasia and a few calcifications are present.

Source:

Close

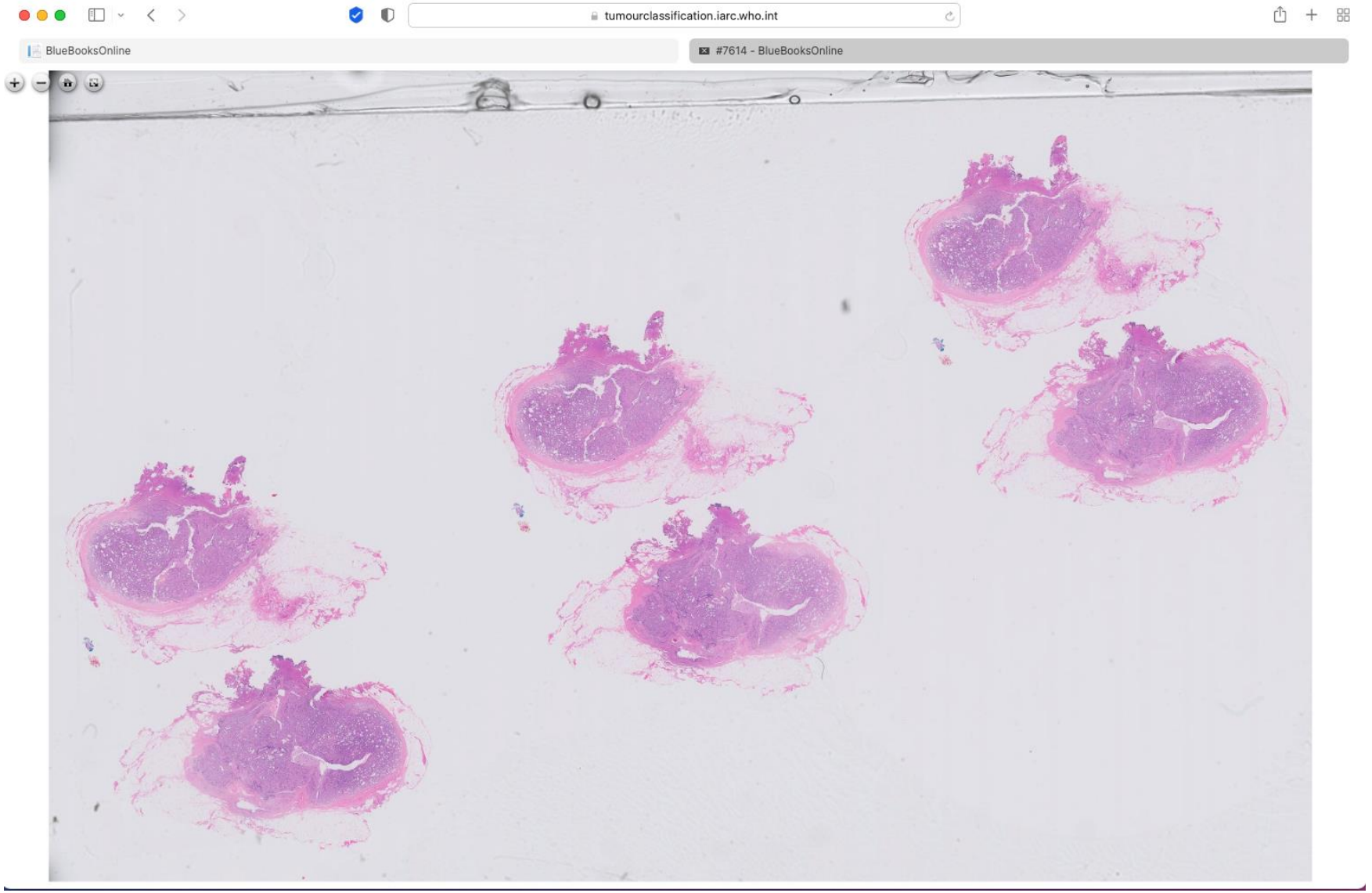


#7614

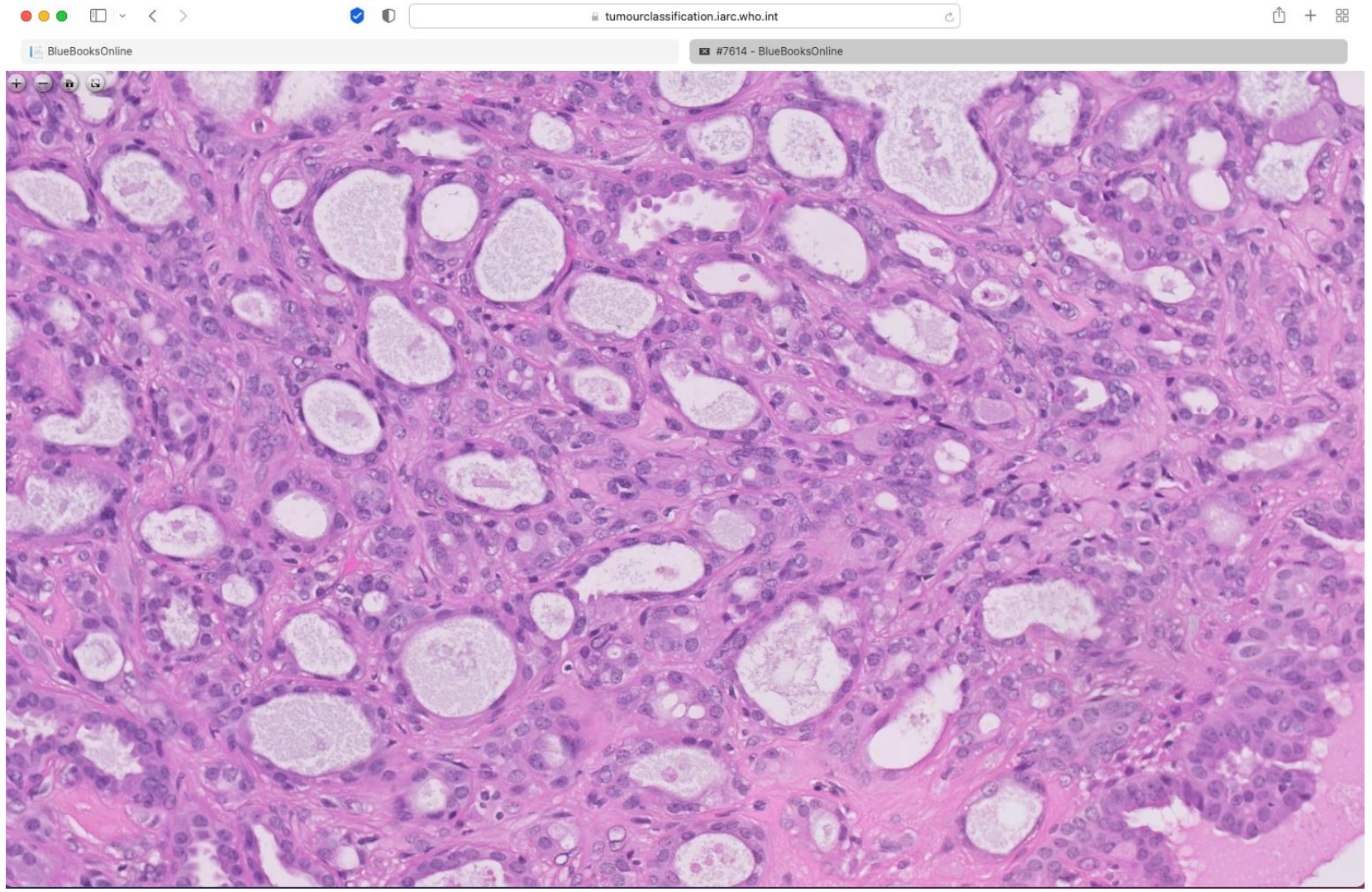


#1854
Ductal adenoma

WHO Classification of Tumours Online: tumourclassification.iarc.who.int



WHO Classification of Tumours Online: tumourclassification.iarc.who.int

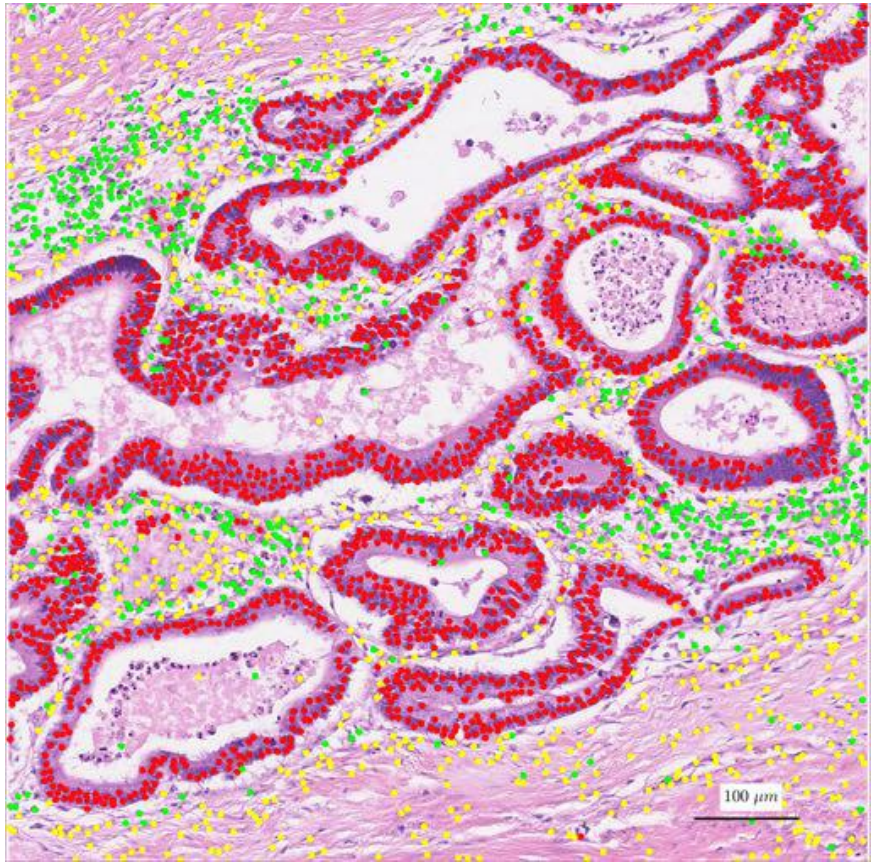


International Agency for Research on Cancer

World Health Organization

AI tools becoming available

- Image analysis tools developed from 1980s to present day.
- Storage now simple
- Machine learning technologies
- Slide scanning technology available!



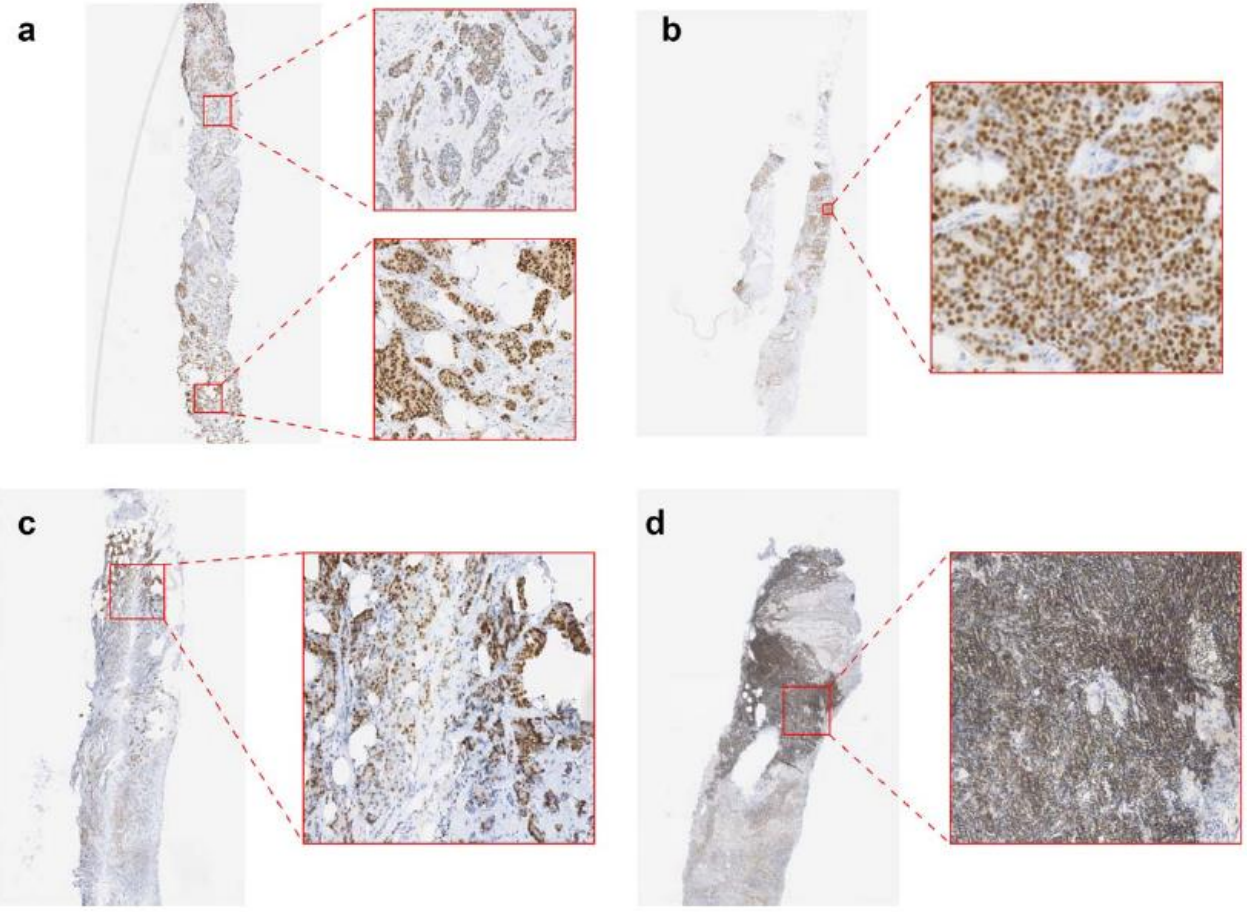
Siriniukunwattana K, et al. IEEE Transactions 2016.

Detected epithelial, inflammatory and fibroblast nuclei are represented as red, green, and yellow dots,

The problem of artefacts…

Or why you still need the pathologist!

Heterogeneous staining.



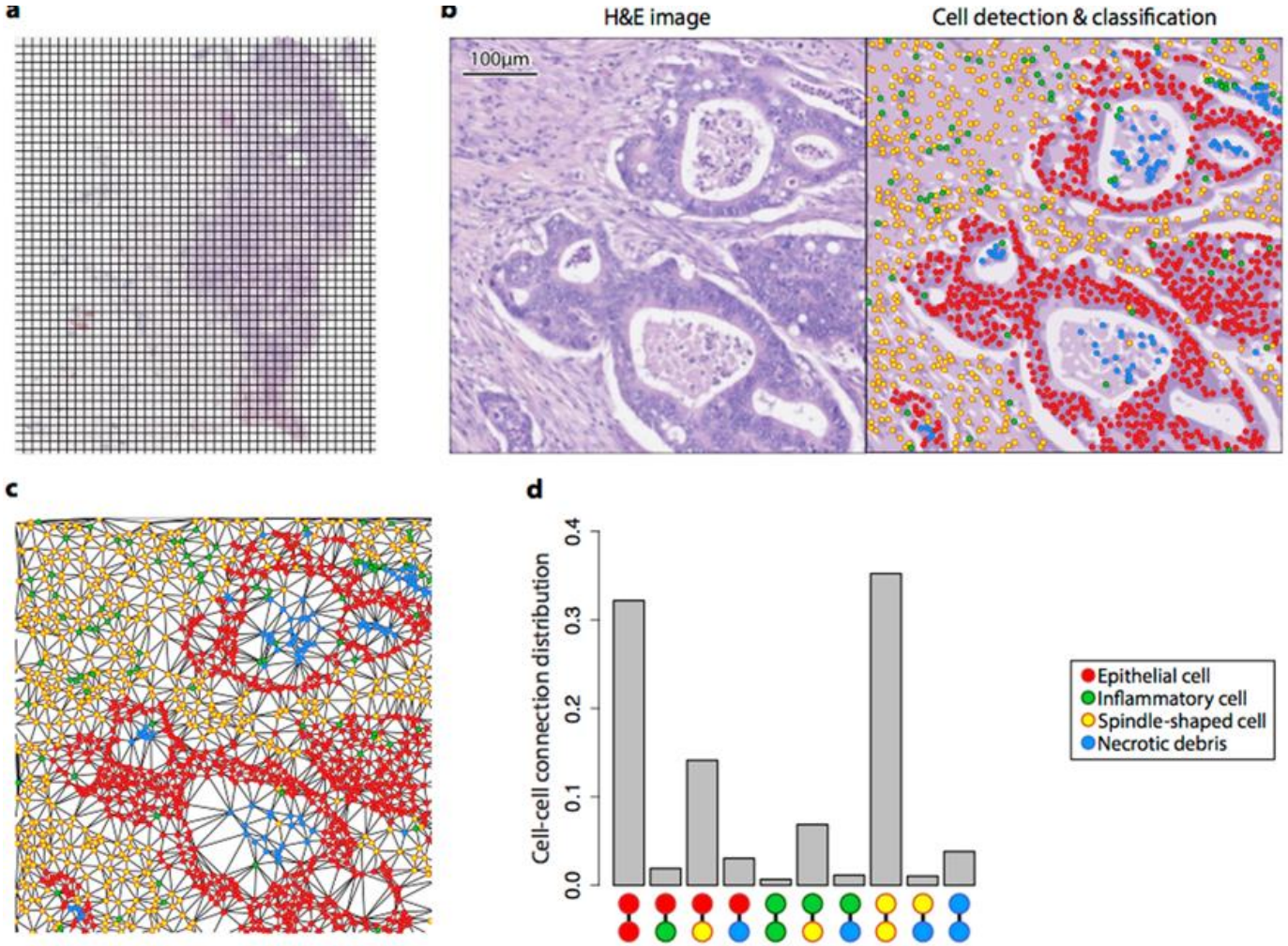
Out of focus WSI

Artefactual shadow

Coverslip problem

Trahearn N, Tsang YW, Cree IA, Snead D, Epstein D, Rajpoot N. Simultaneous automatic scoring and co-registration of hormone receptors in tumor areas in whole slide images of breast cancer tissue slides. Cytometry A. 2017; 91(6): 585-594.

Measuring cellular interaction



Sirinukunwattana K, Snead D, Epstein D, Aftab Z, Mujeeb I, Tsang YW, Cree I, Rajpoot N. Novel digital signatures of tissue phenotypes for predicting distant metastasis in colorectal cancer. Sci Rep. 2018 Sep 12;8(1):13692.

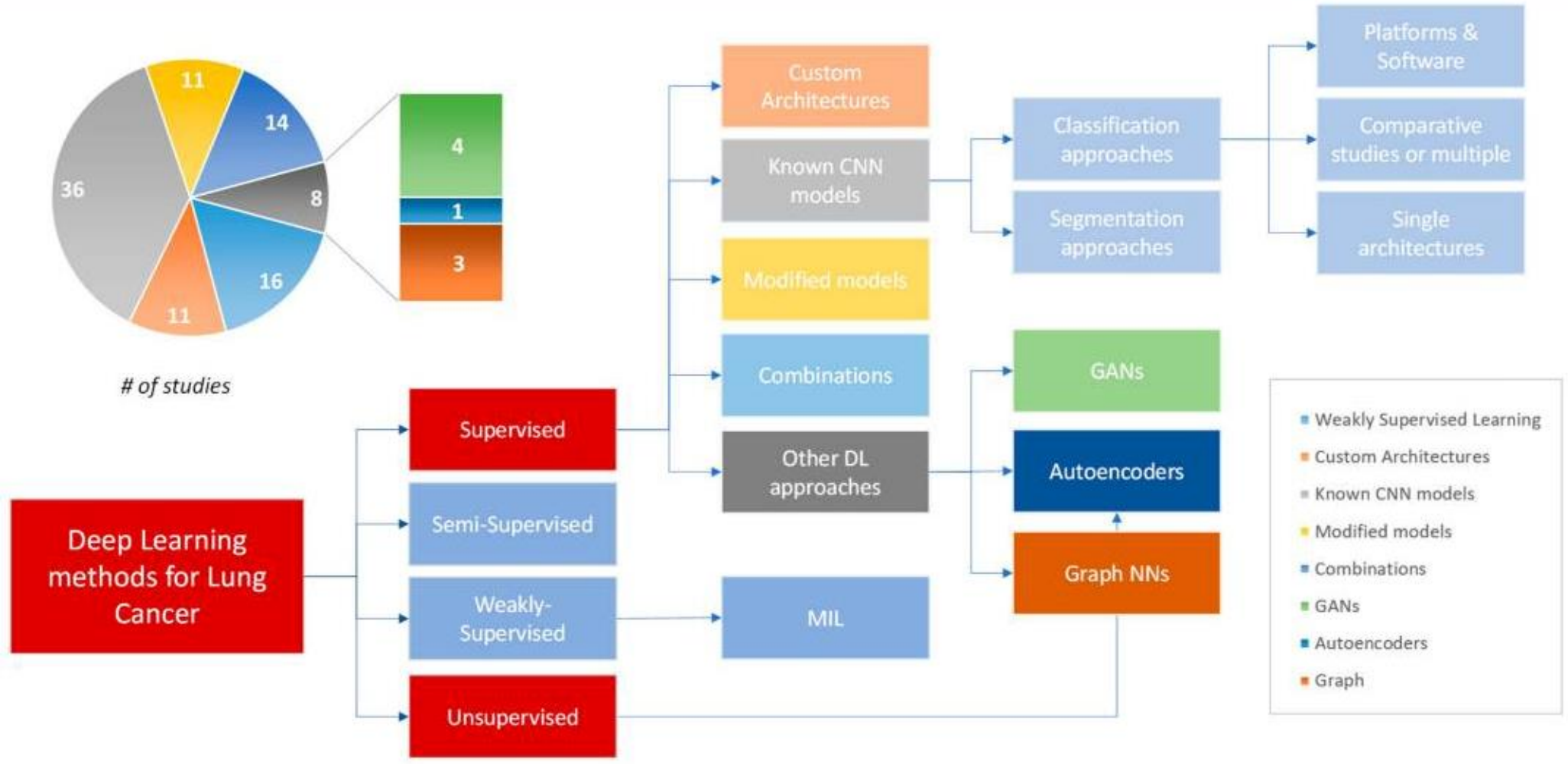
What measurements do pathologists need?

- Planimetry – e.g. margins, depth for staging
- Grade
  - Proliferation (Mitoses, Ki67)
  - Nuclear shape characteristics
  - Architecture (e.g. structure of glands)
  - Others?
- Score for immunohistochemistry – ER, PR, HER2

What measurements might they need?

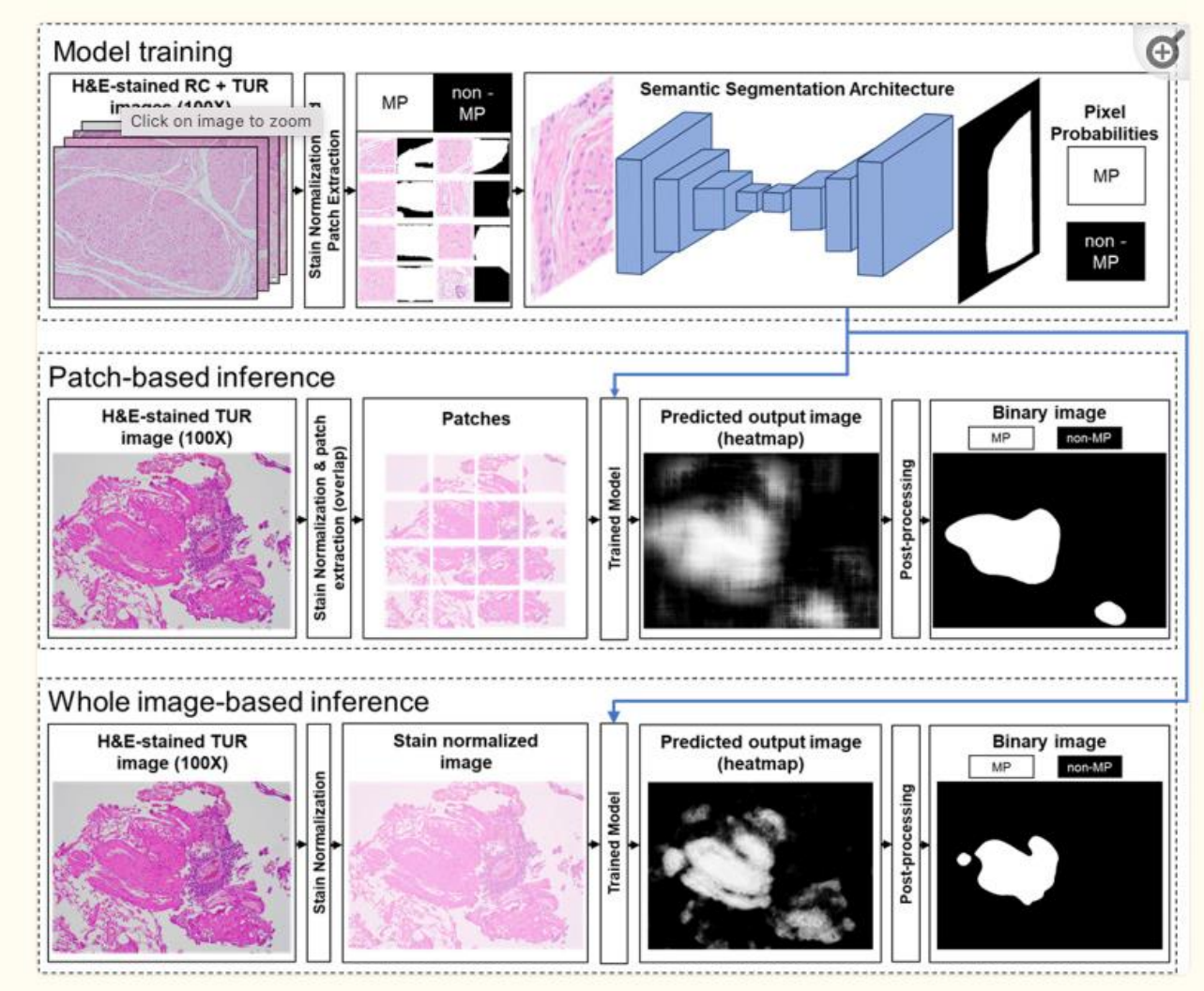
- Tumour infiltrating lymphocytes (Breast tumours, WHO BB 2019 – prognosis)
- Vascularity – microvessel counts (Uveal melanoma, WHO BB 2018 – prognosis)
- Immunohistochemistry – PDL1, others?
- Co-localization
- Percentage neoplastic cell content
- Lymphovascular and perineural invasion
- Dysplasia scoring
- Diagnostic assistance - e.g. finding abnormalities, or excluding malignancy
- Predictive methods for personalised therapy
- Prognosis scoring

Rapid translation to practice - lung cancer



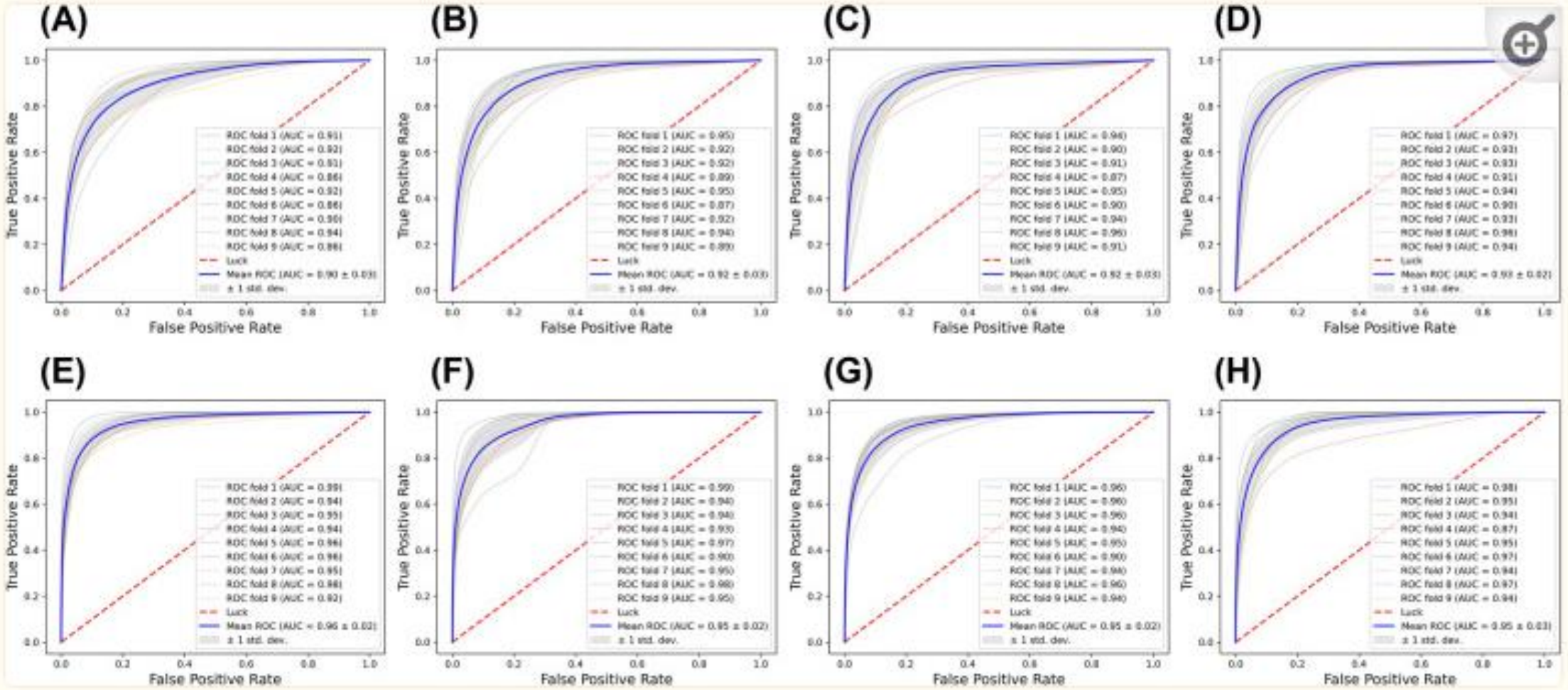
Davri A, Birbas E, Kanavos T, Ntritsos G, Giannakeas N, Tzallas AT, Batistatou A. Deep Learning for Lung Cancer Diagnosis, Prognosis and Prediction Using Histological and Cytological Images: A Systematic Review. Cancers (Basel). 2023 Aug 5;15(15):3981. PMID: 37568797

Bladder cancer



Subramanya SK, Li R, Wang Y, Miyamoto H, Cui F. Deep learning for histopathological segmentation of smooth muscle in the urinary bladder. BMC Med Inform Decis Mak. 2023 Jul 15;23(1):122. PMID: 37454065

Bladder cancer



Subramanya SK, Li R, Wang Y, Miyamoto H, Cui F. Deep learning for histopathological segmentation of smooth muscle in the urinary bladder. BMC Med Inform Decis Mak. 2023 Jul 15;23(1):122. PMID: 37454065

What is needed for translation?

- Need to ensure studies control sources of uncertainty – particularly pre-analytical issues.
- Need for sample size calculations and adequate controls.
- Direct comparison with existing technology – ideally a ‘gold standard’ using PICO (Population, intervention, comparator, outcome) designs.
- Description of patient sets – what are likely biases?
- Use guidance for publication of results – EQUATOR
- Need for good quality meta-analysis and systematic reviews – PROSPERO, PRISMA

Conclusions

- Digital pathology is ready for clinical use and of proven benefit.
- It will produce data to show which diagnostic criteria are robust and reproducible.
- Evidence, rather than opinion, is required for translation: including comparative validation studies in multiple centres.
- Study design is key to success.
- Health economic arguments need to be won with data…
- Consensus is not enough – we need systematic reviews and high quality studies to underpin guidance.
- Some implementation can occur through the WHO Classification of Tumours.

- Computational pathology is here and ready to disrupt histopathologists' cosy way of life
- But they won't have sore necks any more….

Thank you!

- David Snead (UHCW)
- Tim Wing (GE Healthcare)
- Richard Savage (Warwick)
- Nasir Rajpoot (Warwick)
- Victor Sanchez
- Nick Trahearne
- Korsuk Sirinukunwattana