The WHO International Standards for Tumour Classification and Diagnosis

International Agency for Research on Cancer
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International Agency for Research on Cancer

World Health Organization

Declaration of Interests

- I am a pathologist, based at the International Agency for Research on Cancer, part of the World Health Organization

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

IARC - An international effort to combat cancer

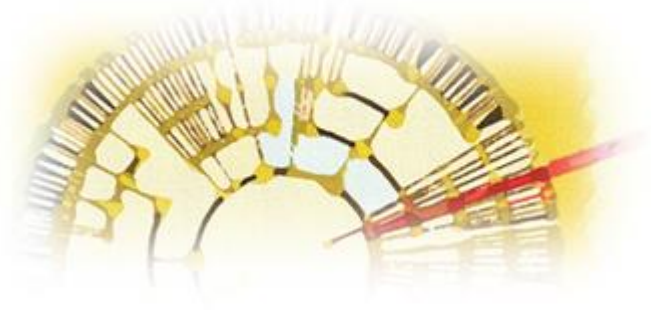
Cancer research for global cancer prevention

IARC and WHO

A complementary partnership

Research IARC on cancer prevention

Evidence-base



for cancer prevention and control programmes

International Agency for Research on Cancer

World Health Organization

World Health Organization

Translates the scientific evidence

into guidelines and policies

IARC – an influential publications programme

International Agency for Research on Cancer

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Classification terms

- *Site*, e.g. Stomach
- *Category*, e.g. Epithelial neoplasms
- *Family* (Class), e.g. Adenomas and other premalignant neoplastic lesions
- *Type*, e.g. Adenoma
- *Sub-Type* (Variant), e.g. Pyloric-gland type

Stage and Grade are dealt with separately….

The WHO Classification of Tumours: International Standards for Cancer Diagnosis

2.0: Tumours of the oesophagus: Introduction

Lam K, Ochiai A, Odze R

This chapter describes benign and tumours of epithelial differentiation a The ICD-O-4 topographical coding s ered in this chapter is presented in Bl common benign lesion, squamous p a dedicated section. Throughout this precursor lesions are typically descr from malignant tumours – a change i decision to make this change was b expansion of our understanding of th cal features of precursor lesions and practice.
There are two main types of precurs gus: Barrett dysplasia and squamou 10 years or so, we have seen an im towards ablation for the treatment patients with high-grade dysplasia. T ally occur in the treatment of low-gr

A (AC)
B (SCC)

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

4 Tumours of the oesophagus

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 & XH9ND6 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

A B

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

Chapter 2

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.

Tumours of the oesophagus 17

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WHO BB Layout (5th Series) DRAFT

- Definition
- ICD-O and ICD11 Codes
- Related Terminology (Synonyms)
- Subtypes
- Localization
- Clinical features and Radiology
- Epidemiology
- Etiology
  - Causes
  - Predisposing factors (Genetics)
- Pathogenesis
- Macroscopic appearance
- Histopathology
  - H&E appearance
  - Immune response & Microenvironment
  - Vascularity
  - Invasion (e.g. PNI)
  - Immunohistochemistry
  - Differential diagnosis
- Cytology
- Molecular pathology
  - Somatic genetics
  - Gene expression
  - Protein expression
  - Tumour markers
- Diagnostic criteria – essential and desirable
- Staging (UICC TNM)
- Prognosis and Prediction
  - Prognostic factors
  - Predictive biomarkers
- Links to other resources
  - ICCR reporting guidance
  - TNM (UICC)

The 5th Series WHO Classification of Tumours

- Digestive System Tumours
- Breast Tumours
- Soft Tissue and Bone Tumours
- Female Genital Tumours
- Thoracic Tumours
- Central Nervous System Tumours
- Paediatric Tumours
- Urinary and Male Genital Tumours
- Head and Neck Tumours
- Endocrine Tumours
- Haematolymphoid Tumours
- Skin and Adnexa Tumours
- Eye and Orbit Tumours
- Neuroendocrine Tumours
- Hereditary Tumours

http://whobluebooks.iarc.fr

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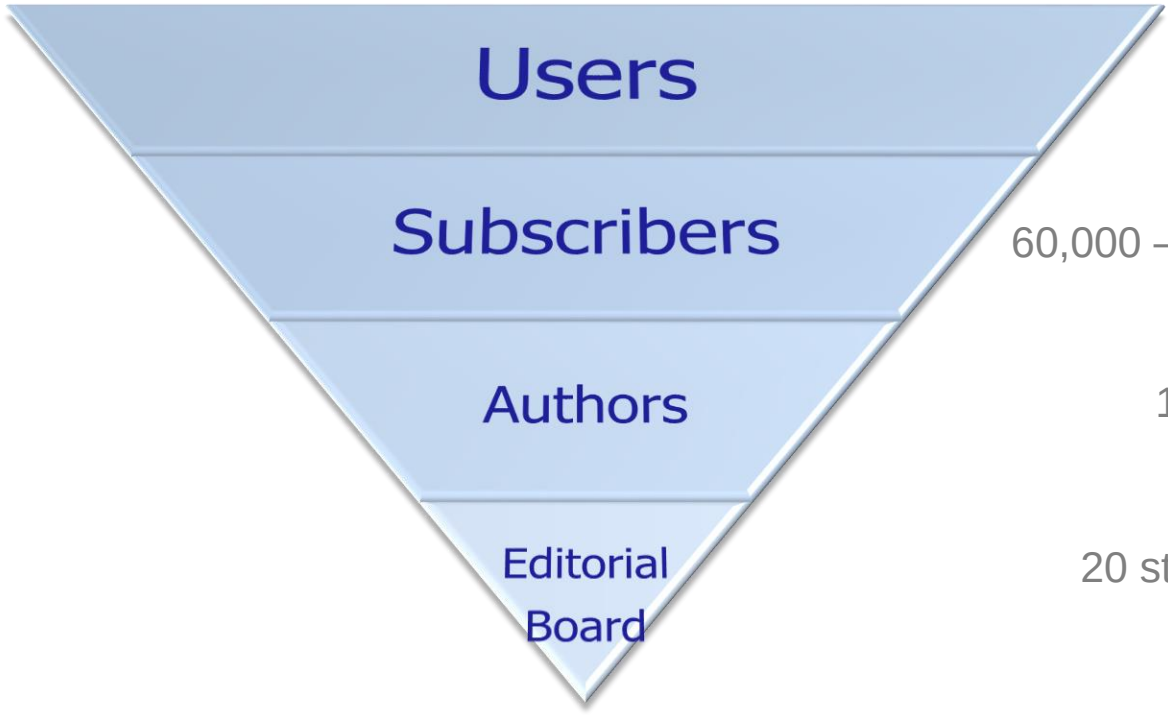
WHO Blue Books
Faculty



300,000 (estimate)

60,000 – mainly pathologists

1,800 (150 per book)

20 standing + 144 expert

WCT Blue Books team

WHO Classification of Tumours - *ONLINE*

Now available at: tumourclassification.iarc.who.int

Instant access to the following books:

5th edition

Digestive Tumours
Breast Tumours
Soft Tissue and Bone - beta

4th edition

Eye Tumours
Skin Tumours
Endocrine Tumours
Head and Neck Tumours
Central Nervous System - update

Special subscription rate of *100 Euros*

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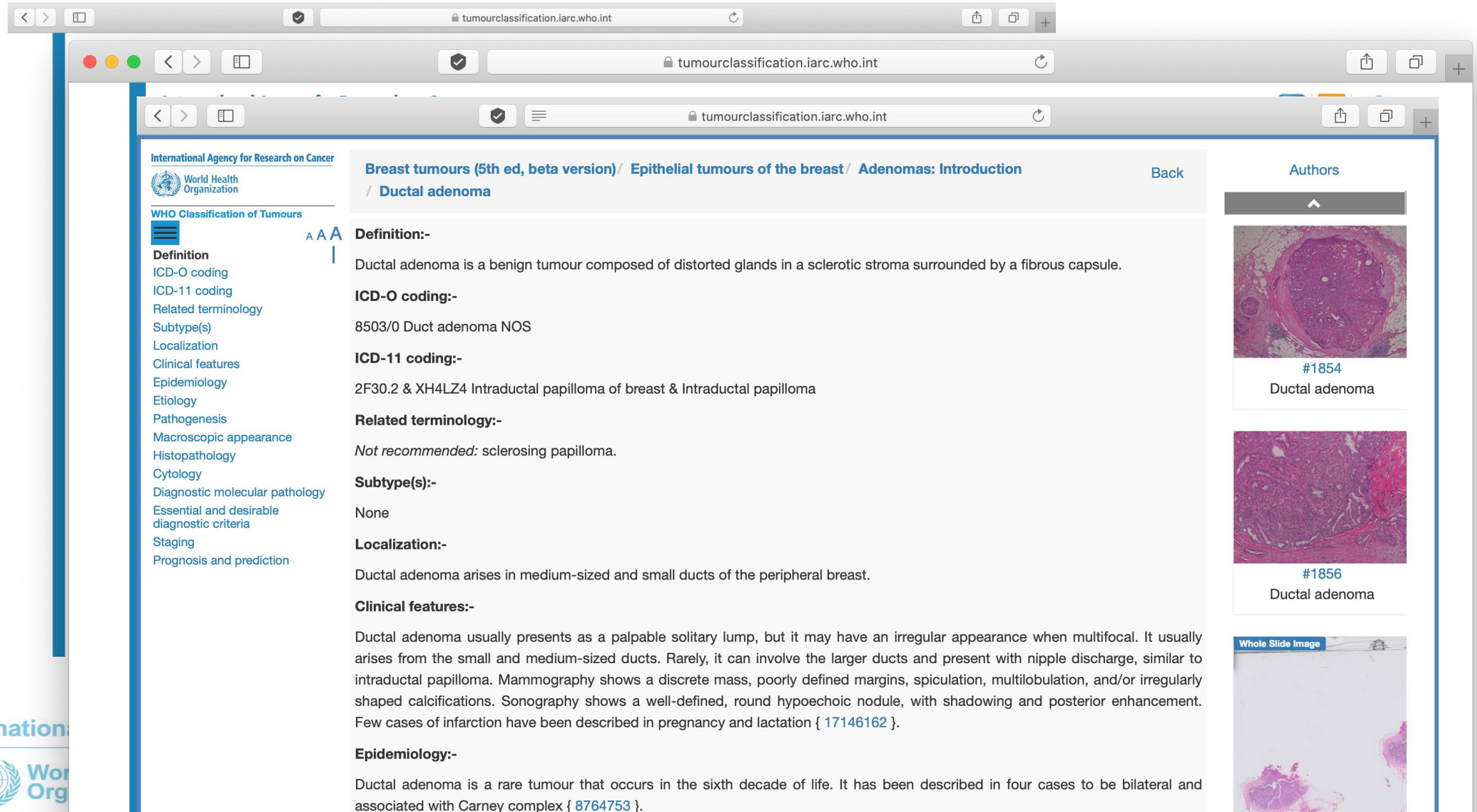


#7614

View WSI

Diagnosis:

Legend:

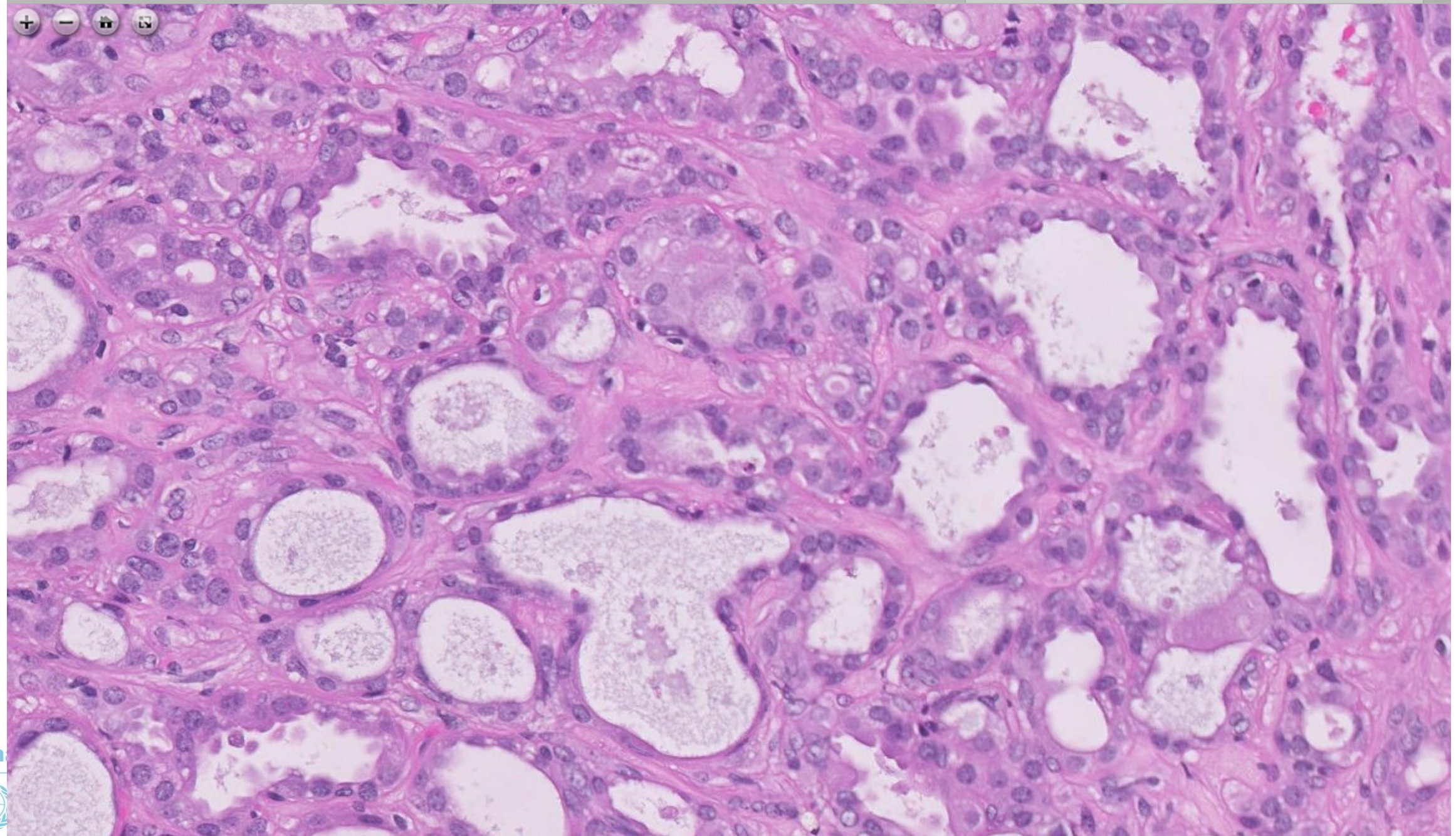
Ductal adenoma consists of an encapsulated solid nodule of round and oval glands within fibrous stroma. Apocrine metaplasia and a few calcifications are present.

Source:

Tan PH, and Wong C, Sng A, Koh V, Heng SY.

Division of Pathology, Singapore General Hospital

Close



Digital Pathology:
Intuitive, Easy To Use, Automatic

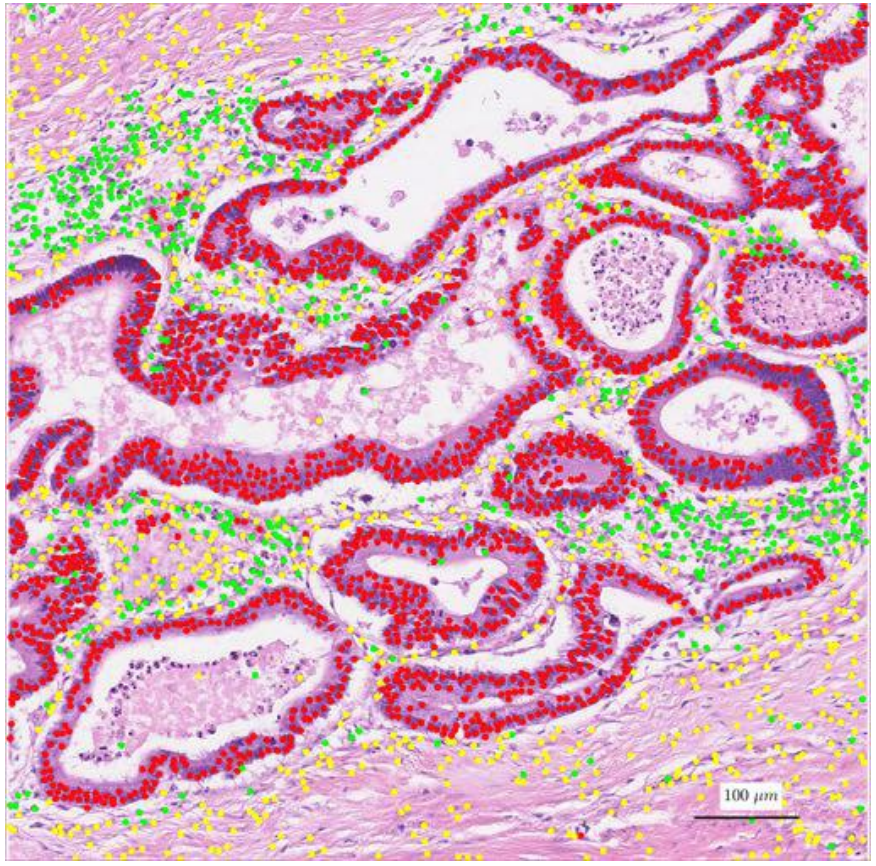
Validation study

- 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.

AI tools becoming available

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



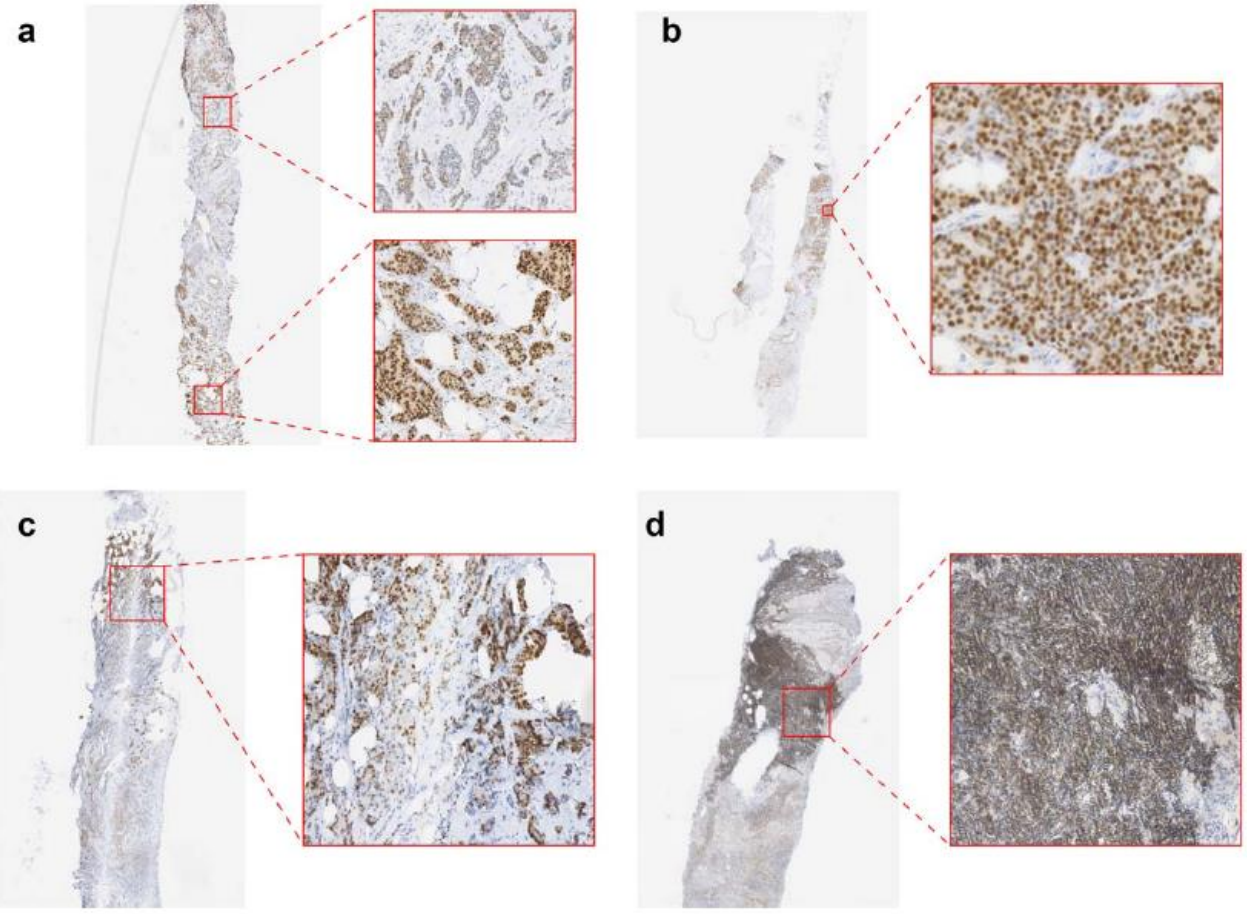
Siriniukunwattana K, et al. IEEE Transactions 2016.

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.



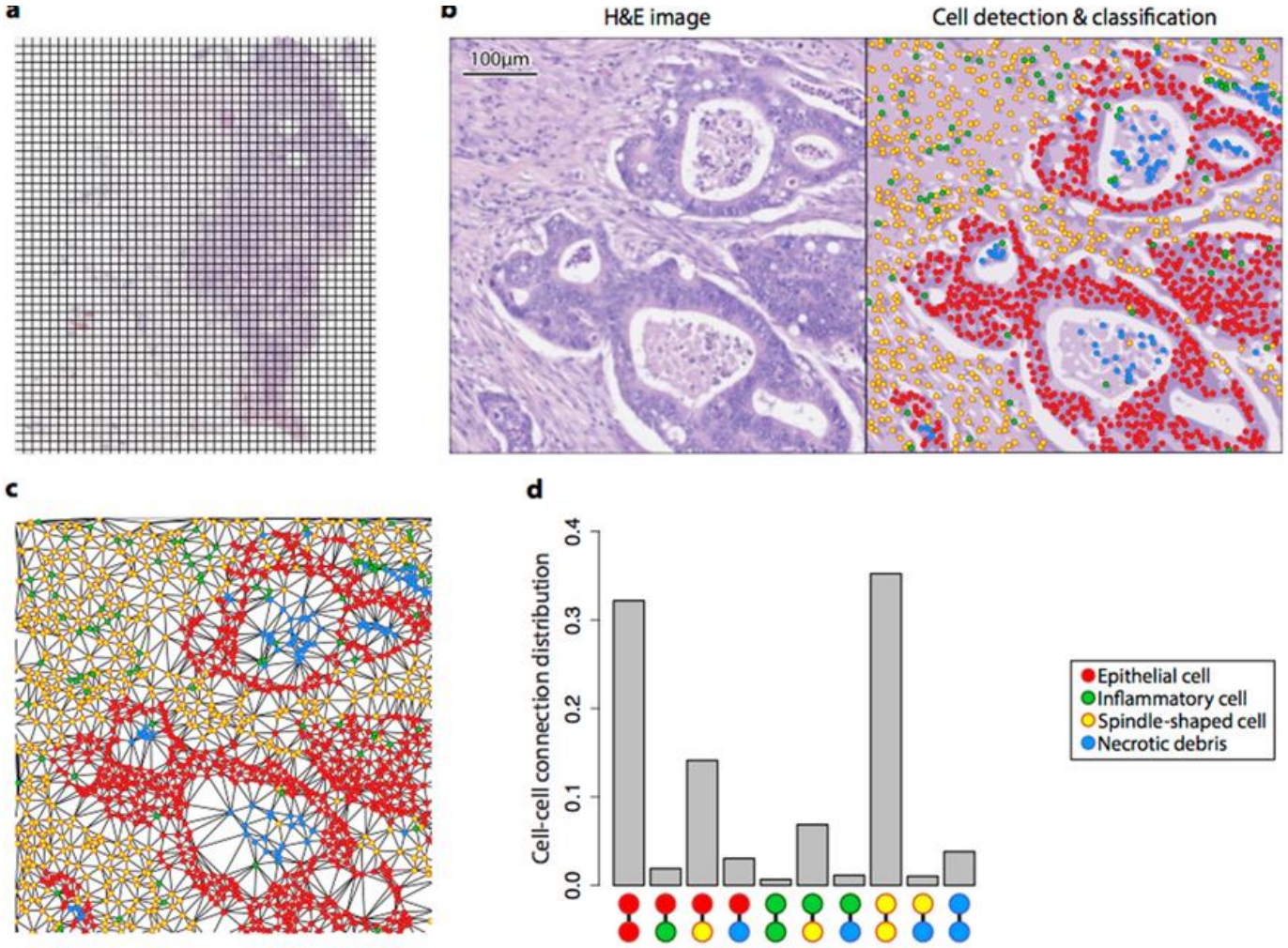
Out of focus WSI

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 of melanoma, etc…
- Grade
  - Proliferation (Mitoses, Ki67) per mm^2
  - Nuclear shape characteristics
  - Architecture (e.g. structure of glands)
- Score for immunohistochemistry – ER, PR, HER2, PDL1
- Co-localization – what's staining?
- Tumour infiltrating lymphocytes (Breast tumours, WHO BB 2019 – prognosis only)
- Vascularity – microvessel counts (Uveal melanoma, WHO BB 2018 – prognosis only)
- Percentage neoplastic cell content (for molecular pathology)
- Lymphovascular and perineural invasion
- Dysplasia scoring

What is needed for translation to practice?

Quality:

- Studies should control sources of uncertainty – particularly pre-analytical issues.
- 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 network
- Effectiveness data – health economics
- Need for evaluation of evidence: meta-analysis and systematic reviews – PROSPERO, PRISMA

The International Collaboration for Cancer Classification and Research (IC^{3}R)

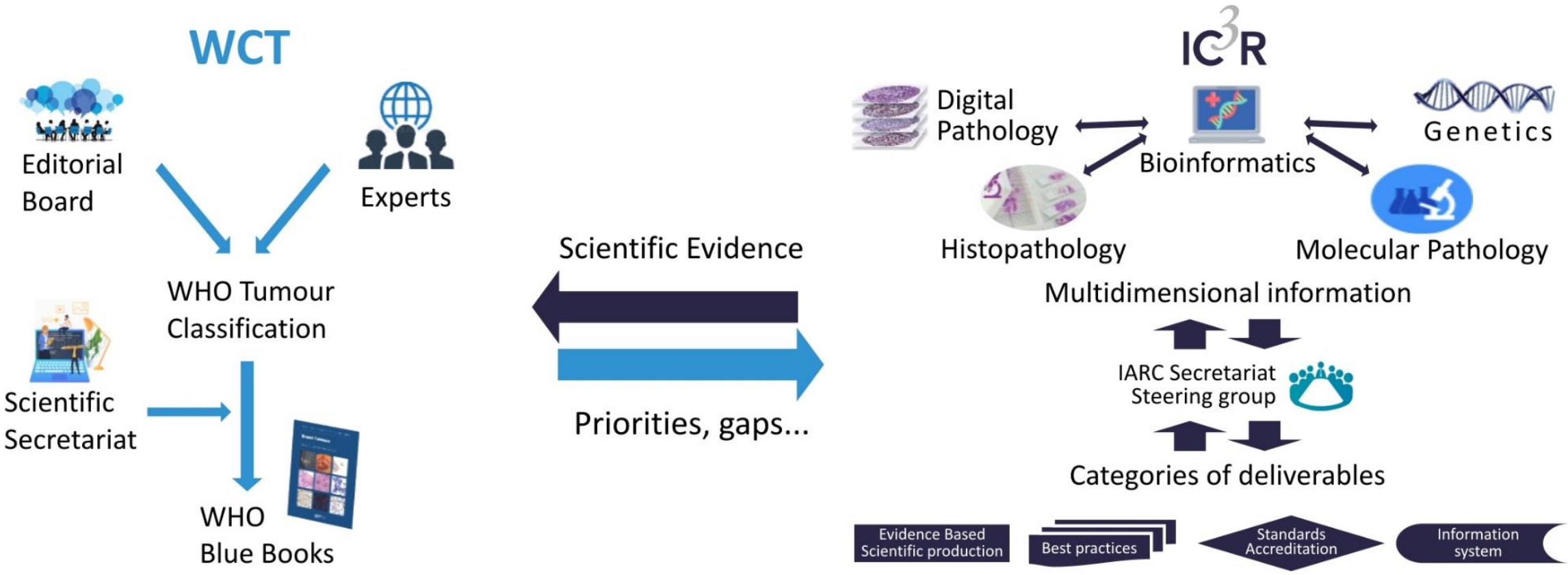
IC^{3}R will provide a forum for encouraging high quality research, and for coordinating evidence generation, synthesis, and evaluation, for tumour classification. Member institutions include universities, research centres and other interested parties, that will assign representatives to discuss and coordinate international efforts for the provision of high level, up-to-date evidence and the promotion of universal standards to underpin the WHO Classification of Tumours.

IC3R collaboration for cancer classification

International Agency for Research on Cancer

World Health Organization

IC^{3}R Framework



How to help?

- Provide the evidence: research
- Evaluate the evidence: systematic review
- Fund the evidence: buy the books or the website?

- Let us know what you think – feedback, cases, errors

Conclusion

- There is a need for all cancer diagnosticians to contribute to research, to gather the evidence our patients need, and to evaluate that evidence for use in their practice.
- Our diagnoses underpin the management of individual patients, cancer research, and epidemiology.
- Implementation of academic research in pathology is largely through the WHO Blue Books, which provide the international standards for diagnosis.
- We have a joint responsibility to ensure their accuracy.

Thank you!

The Nouveau Centre – opening in 2022