Multidisciplinary tumour classification: implications for diagnosis

Honorary Professor of Pathology,

Institute of Ophthalmology,

University College London, UK

Declaration of Interests

- Honorary Professor of Pathology, Institute of Ophthamology, 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.

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

Learning points

- Understand the need for a hierarchical classification of tumours to underpin diagnosis.
- Appreciate that each discipline views the classification a different way: the classification requires a multidimensional approach.
- Realise the key contributions of different diagnostic specialties to tumour diagnosis.
- Appreciate the need for research and levels of evidence for the 6th edition, starting later next year.

CAROLI LINNÆI

EQUITIS DE STELLA POLARI,

ARCHIATRI REGII, MED. & BOTAN. PROFESS. UPSAL.;
ACAD. UPSAL. HOLMENS. PETROPOL. BEROL. IMPER.
LOND. MONSPEL. TOLOS. FLORENT. SOC.

SYSTEMA NATURÆ

PER

REGNA TRIA NATURÆ,

SECUNDUM

CLASSES, ORDINES,
GENERA, SPECIES,

CUM

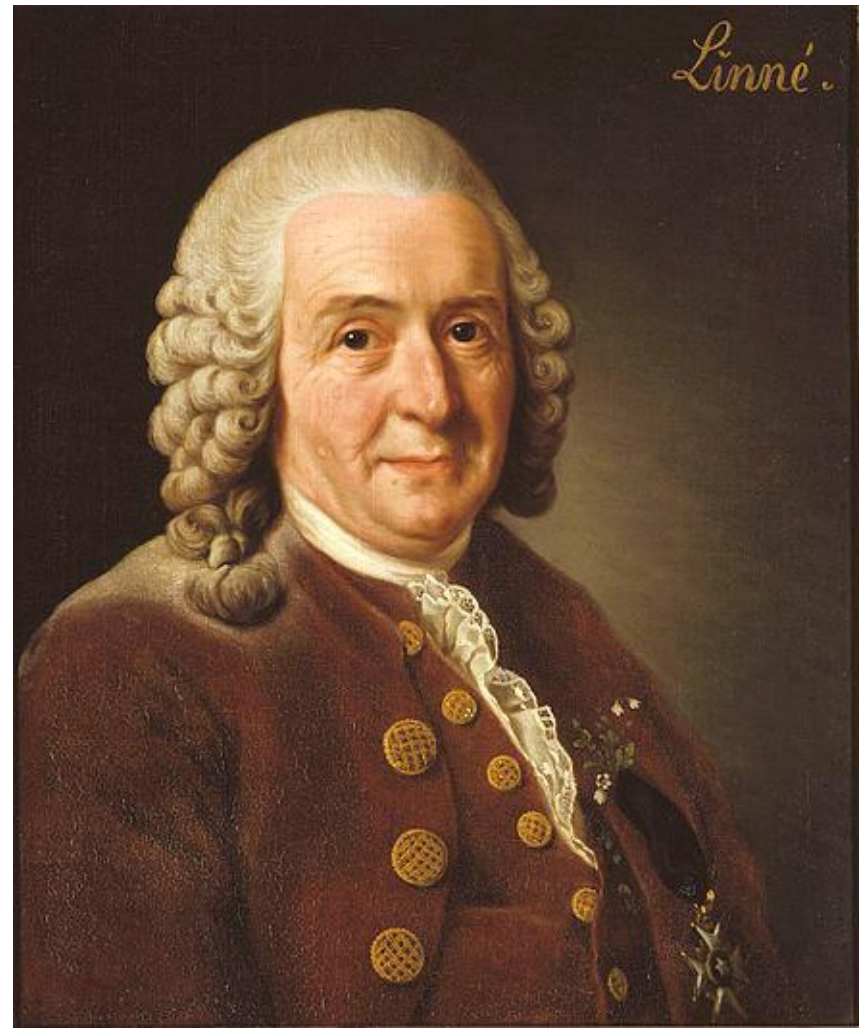
CHARACTERIBUS, DIFFERENTIIS,
SYNONYMIS, LOCIS.

TOMUS I.

EDITIO DECIMA, REFORMATA.

Cum Privilegio S:æ R:æ M:tis Sveciæ.

HOLMIÆ,
IMPENSIS DIRECT. LAURENTII SALVII,
1758.



Carl Linnaeus (1707 – 1778)

- *Taxonomy* is the science of defining and naming groups of biological organisms on the *basis of shared characteristics*

- *Cancer classification* is based on shared characteristics of cancers – currently mainly histology and genetics.

WHA10.18 The Tenth World Health Assembly resolved, '…to continue work on formulating international definitions of nomenclature and statistical classification…' (May 1957)

The taxonomy of tumours

The WHO Blue Books provide a definitive evidence-based classification of all cancer types to enable diagnosis and research worldwide.

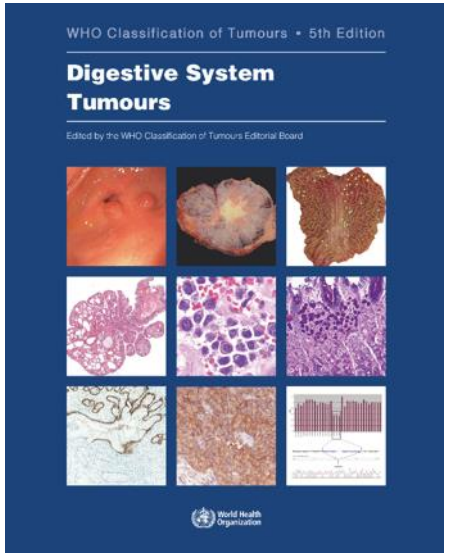
The diagnosis of cancers underpins individual patient treatment, as well as research into all aspects of cancer causation, prevention, therapy, and education.

The WHO Blue Books are not just for pathologists…

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….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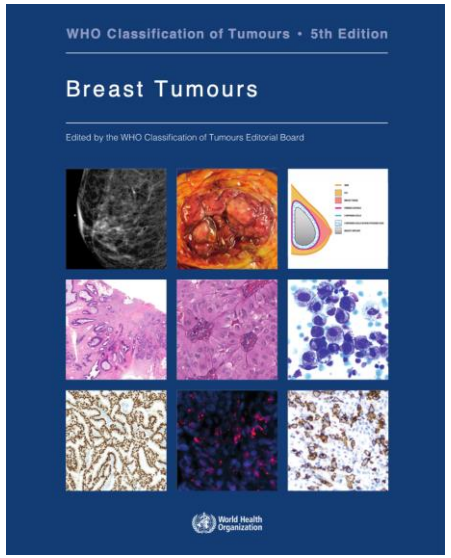
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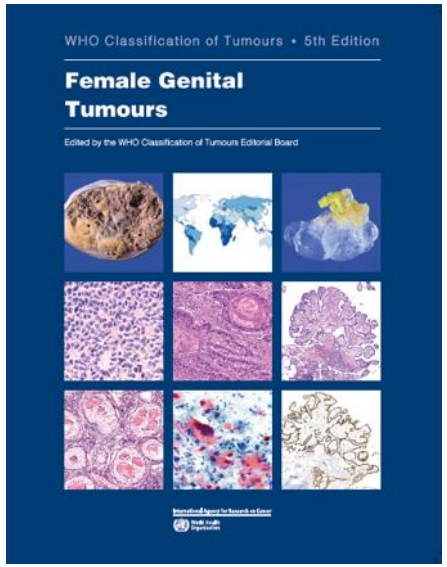
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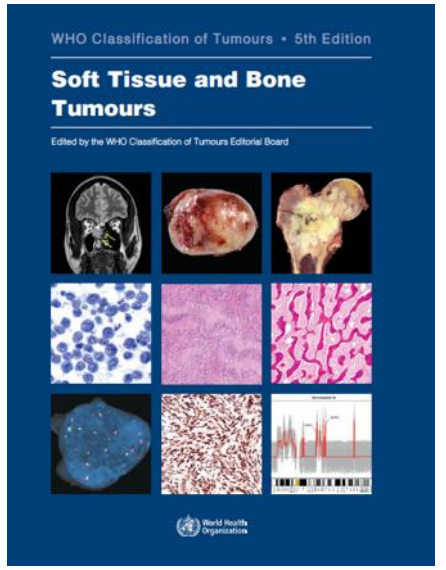
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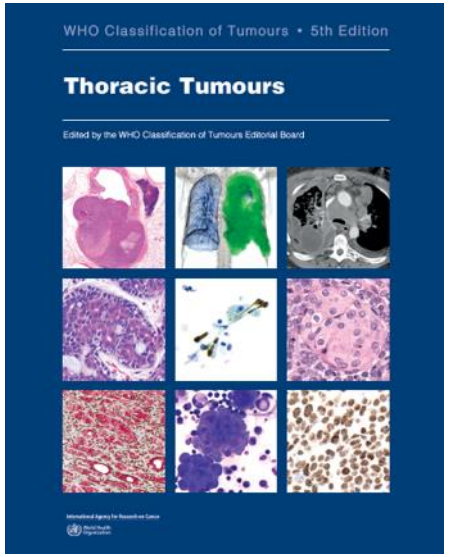
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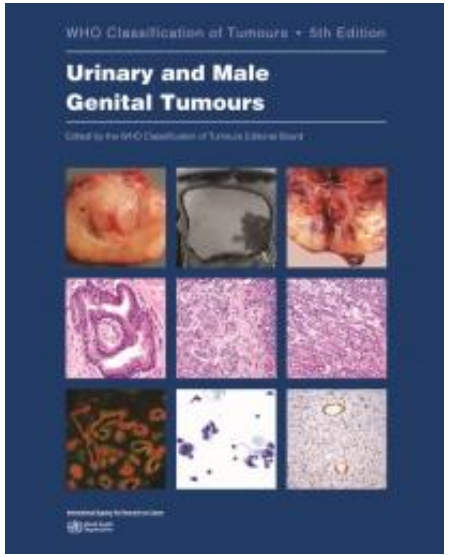
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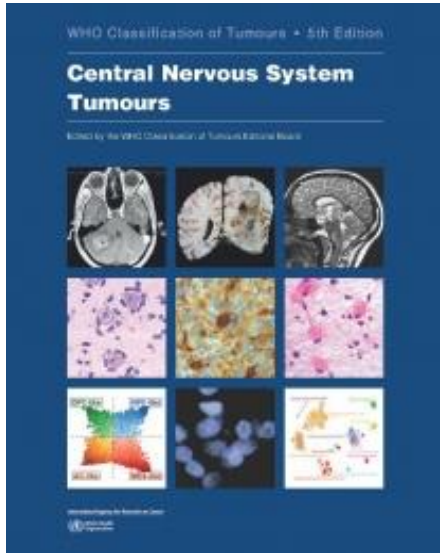
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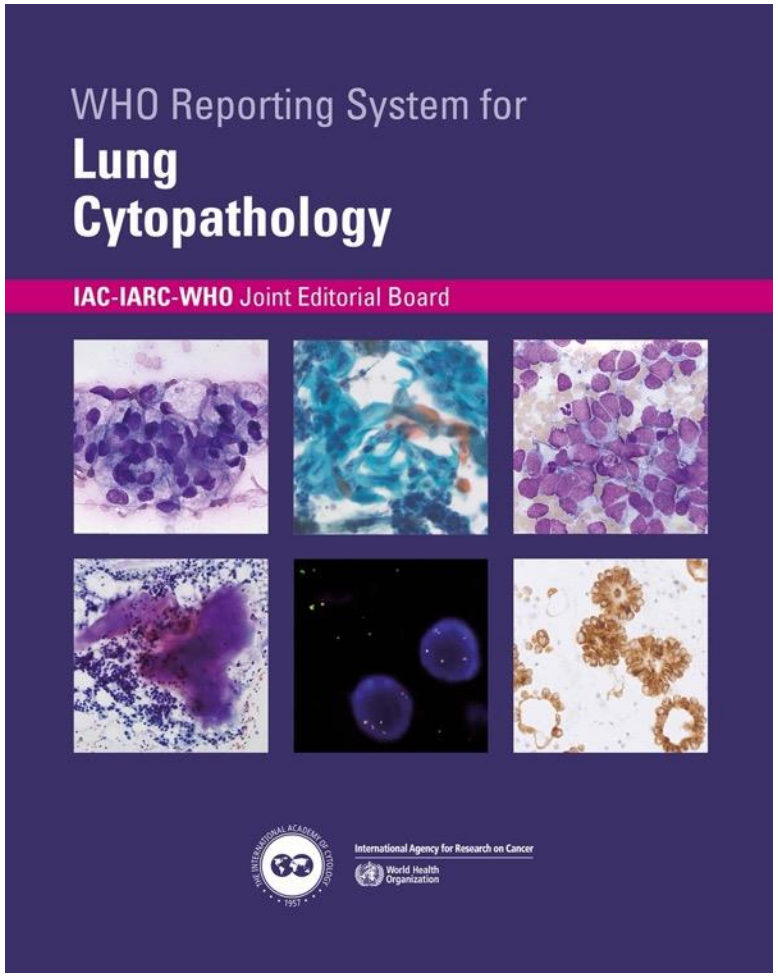
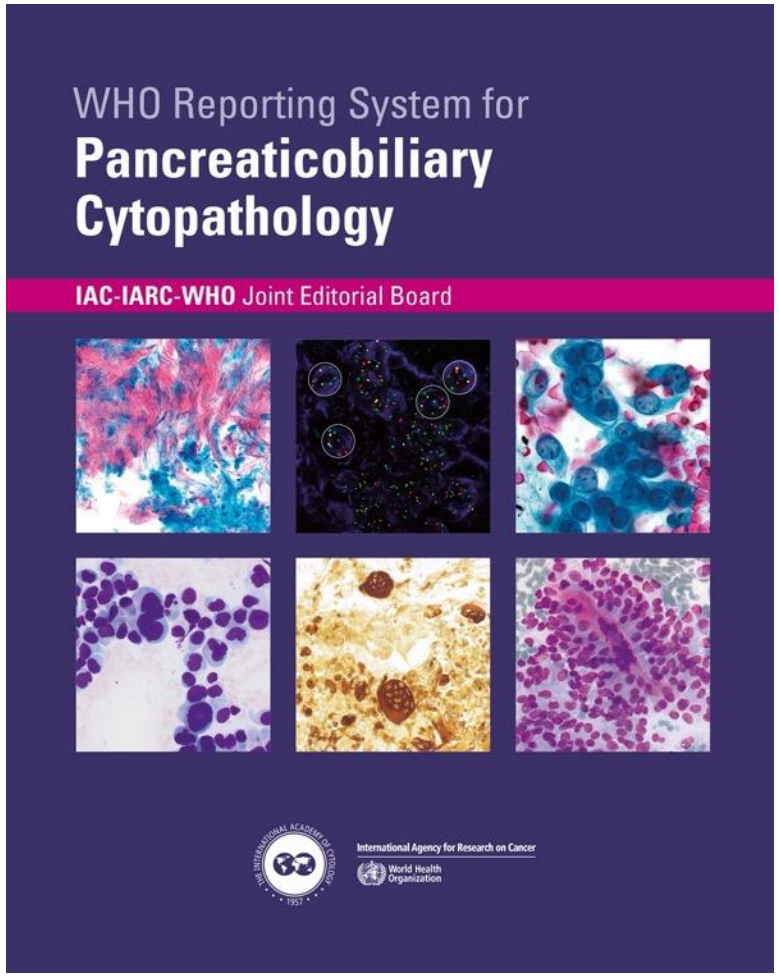




2.0: Tumours of the oesophagus: Introduction

Lam AK
Ochiai AO
Odze R

This chapter describes benign and malignant oesophageal tumours of epithelial differentiation and their precursor lesions. The ICD-O-4 topographical coding for the anatomical sites covered in this chapter is presented in Box 2.XX (p. XXX). The most common benign lesion, squamous papilloma, is addressed in a dedicated section. Throughout this fifth edition of the series, precursor lesions are typically described in separate sections from malignant tumours – a change from the fourth edition. The decision to make this change was based on the considerable expansion of our understanding of the biological and pathological features of precursor lesions and their relevance to clinical practice.

There are two main types of precursor lesions in the oesophagus: Barrett dysplasia and squamous dysplasia. Over the past 10 years or so, we have seen an important shift from surgery towards ablation for the treatment of Barrett oesophagus in patients with high-grade dysplasia. The same shift may eventually occur in the treatment of low-grade dysplasia, but this is currently a cont grade vs high-gr

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

C15 Oesophagus
C15.0 Cervical oesophagus
C15.1 Thoracic
C15.2 Abdominal
C15.3 Upper thir
C15.4 Middle thi
C15.5 Lower thir
C15.7 Gastro-oe
C15.8 Overlappi
C15.9 Oesophag

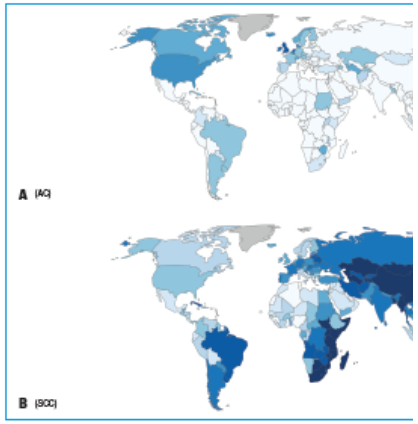


Fig. 2.XX National age-standardized incidence rates (ASRs), per 100 000 person-years, of oesophageal carcinoma cell carcinoma (SCC).

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 intram changes of intrapapillary capillary loops

Epidemiology
The reported prevalence of oesophage varies from 3% in some parts of the wor the countries with the highest prevalenc mous cell carcinoma, such as China ar of Iran [1139]. In series from China, th of squamous dysplasia was mild, follo severe [1139]. Most patients are asympt areas of dysplasia or erosion, as well a cell carcinoma, can cause symptoms s bleeding. The prevalence and sex di dysplasia mirror those of squamous cell dysplasia is most common among patie decades of life [3516].

Etiology
The risk factors for oesophageal sq similar to those for oesophageal squam Box 2.XX, p. XXX).

Pathogenesis
Overexpression of p53 and hyperm (*P16/INK4a*) have been reported in squa

Macroscopic appearance
Squamous dysplasia can appear as a lesion.

Histopathology
The diagnosis of squamous dysplasia of both cytological and architectural at is characterized by nuclear atypia,

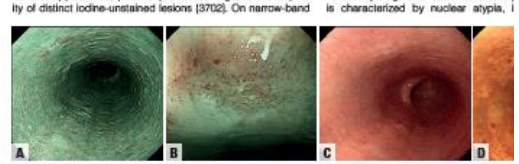


Fig. 2.XX Oesophageal squamous dysplasia. **A** On low-magnification endoscopy with narrow-band imaging, the lesion appears as a brownis the front left wall, 30 cm from the incisor. **B** On high-magnification endoscopy with narrow-band imaging, the intrapapillary capillary loops are between them is brightly coloured. **C** On white-light endoscopy, the lesion appears as a flat, slightly depressed lesion with mild redness. **D** On lesion is positive for the pink-colour sign – it is well demarcated and unstained.

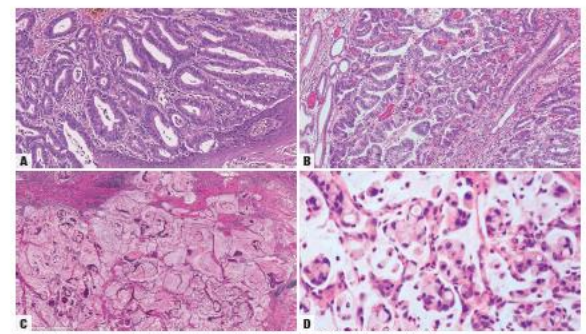


Fig. 2.XX Oesophageal adenocarcinoma. **A** Tubular pattern. **B** Papillary pattern. **C** Mucinous pattern. **D** Signet-ring cell pattern.

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

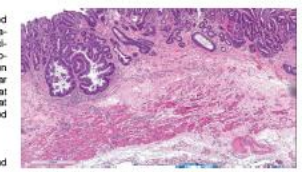
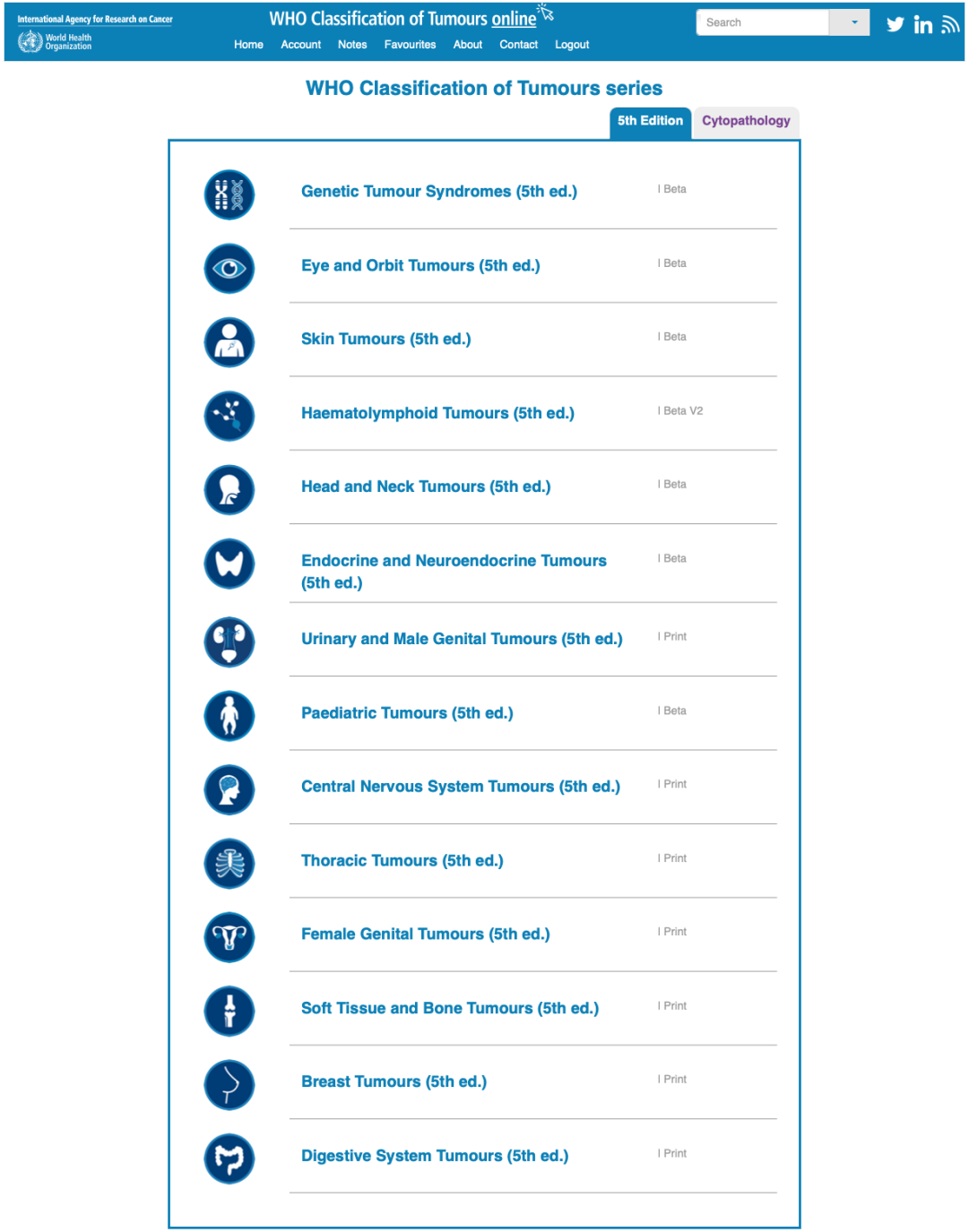
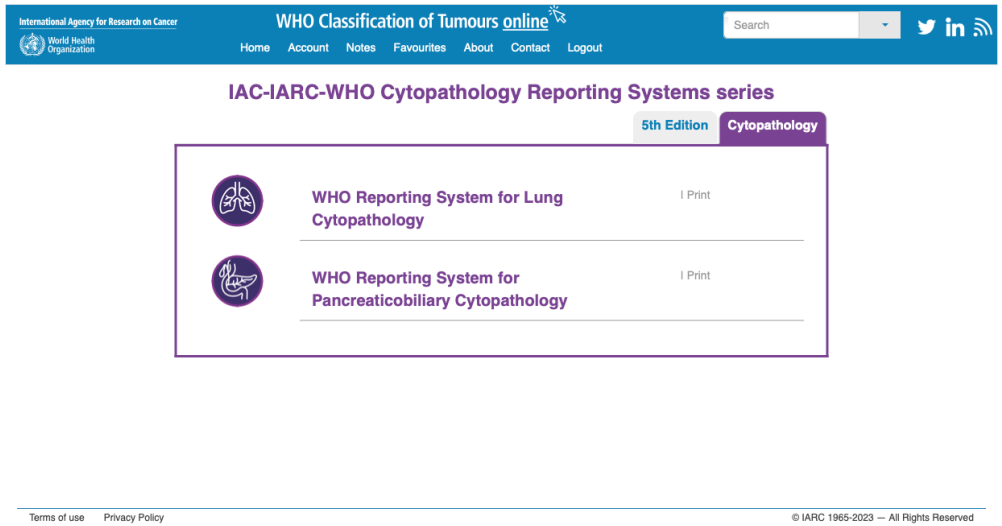


Fig. 2.XX Oesophageal adenocarcinoma. An example in Barrett oesophagus with a double layer of muscularis mucosae.





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Shabnam Jaffer

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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 }.

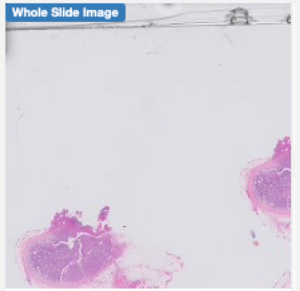
Epidemiology
Ductal adenoma is a rare tumour that occurs in the sixth decade of life. It has been described in four cases to be bilateral and associated with Carney complex { 8764753 }.

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



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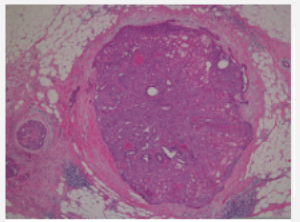
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Ductal adenoma

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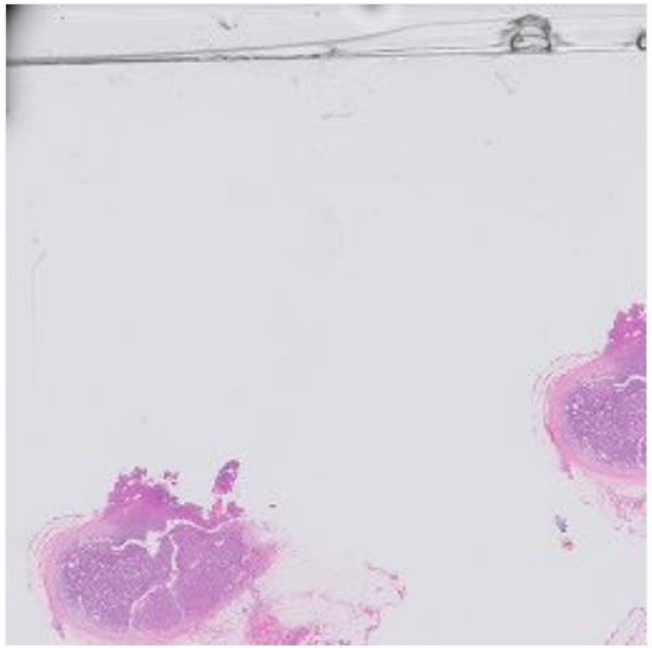
Attachment



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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:

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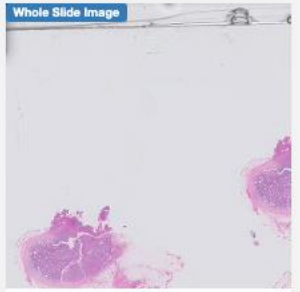

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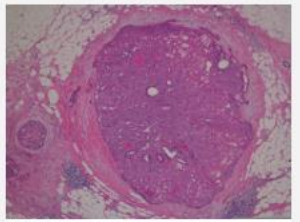

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Ductal adenoma

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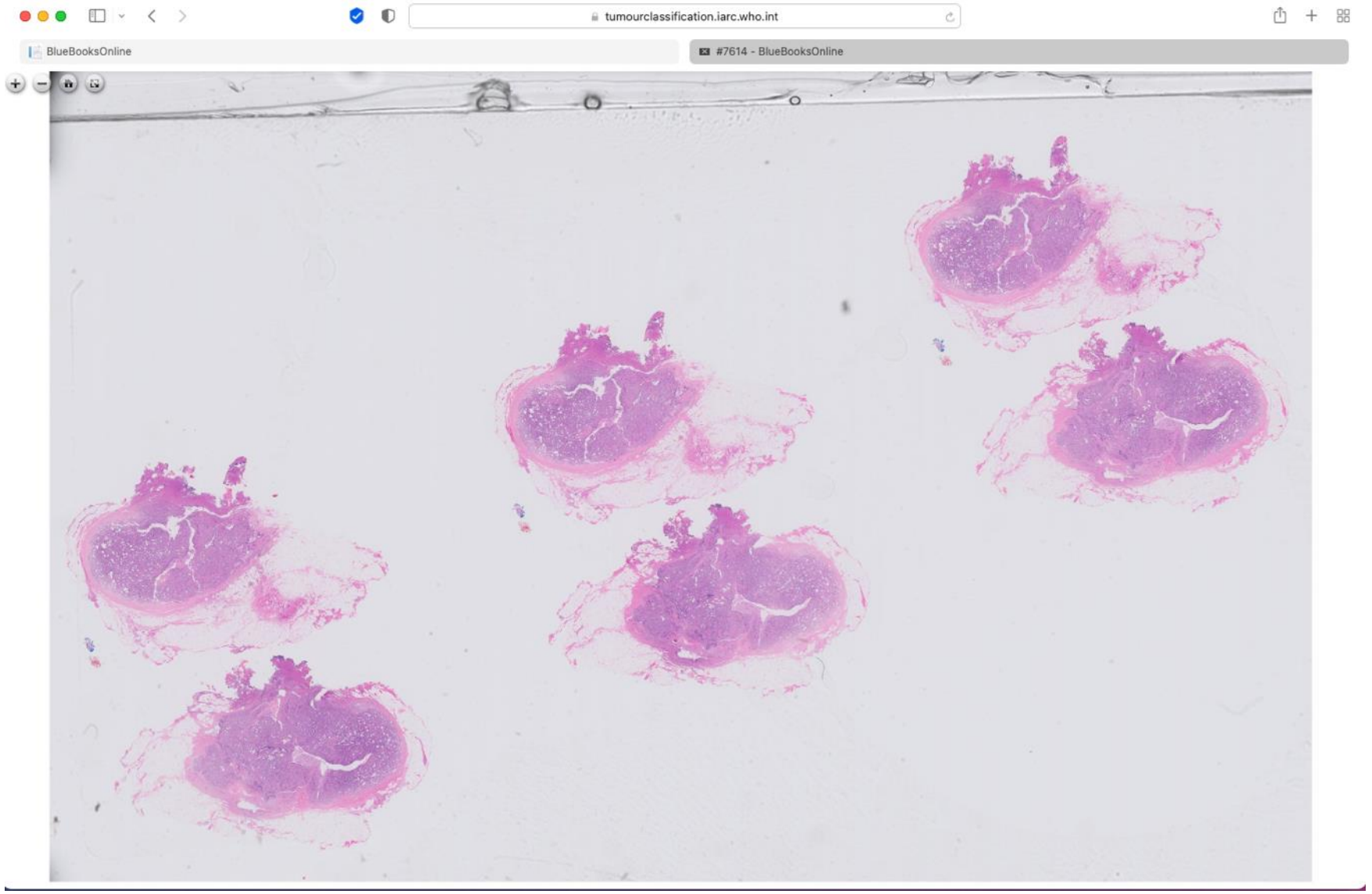

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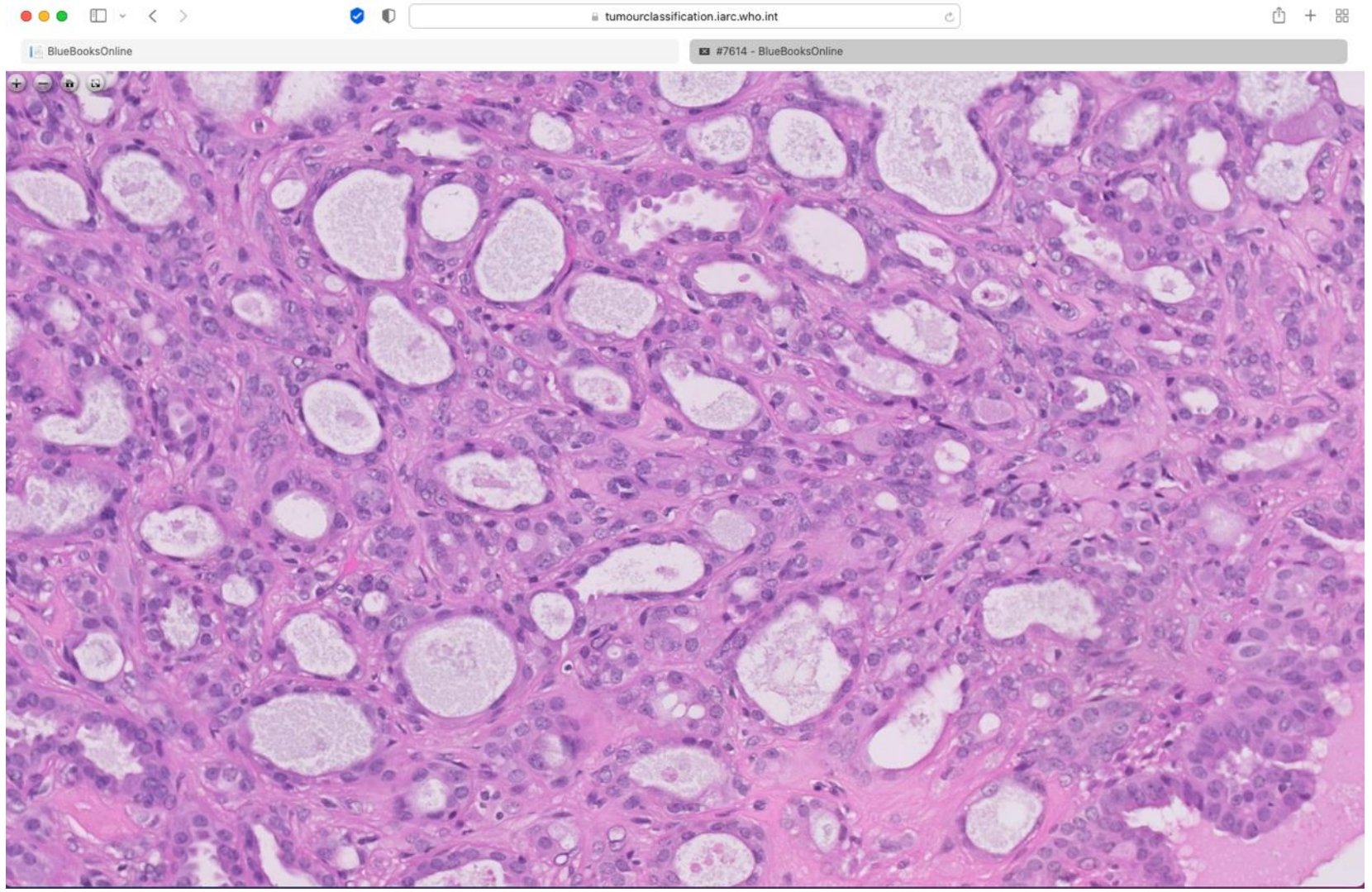
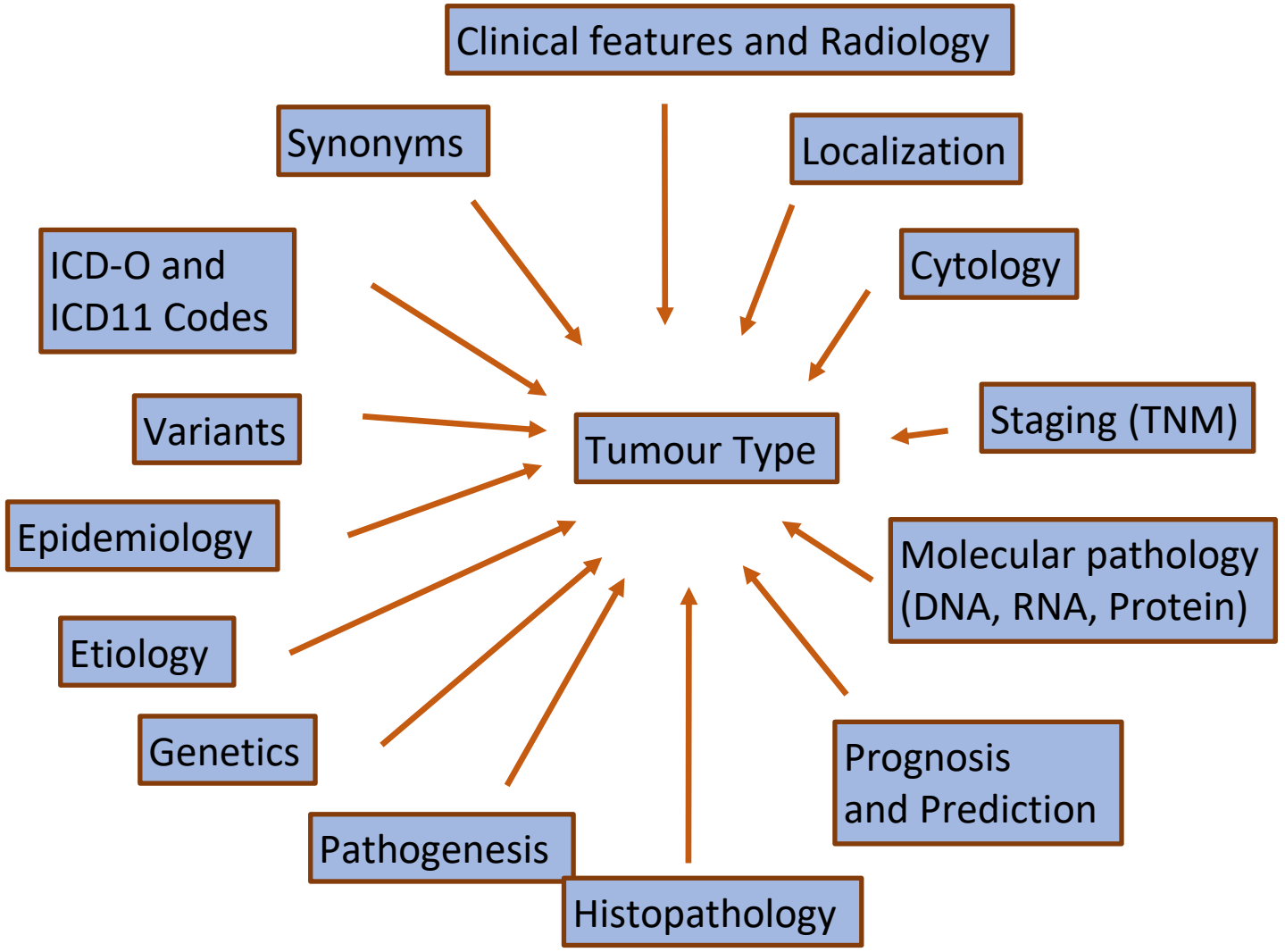


The multi-dimensional nature of cancer classification



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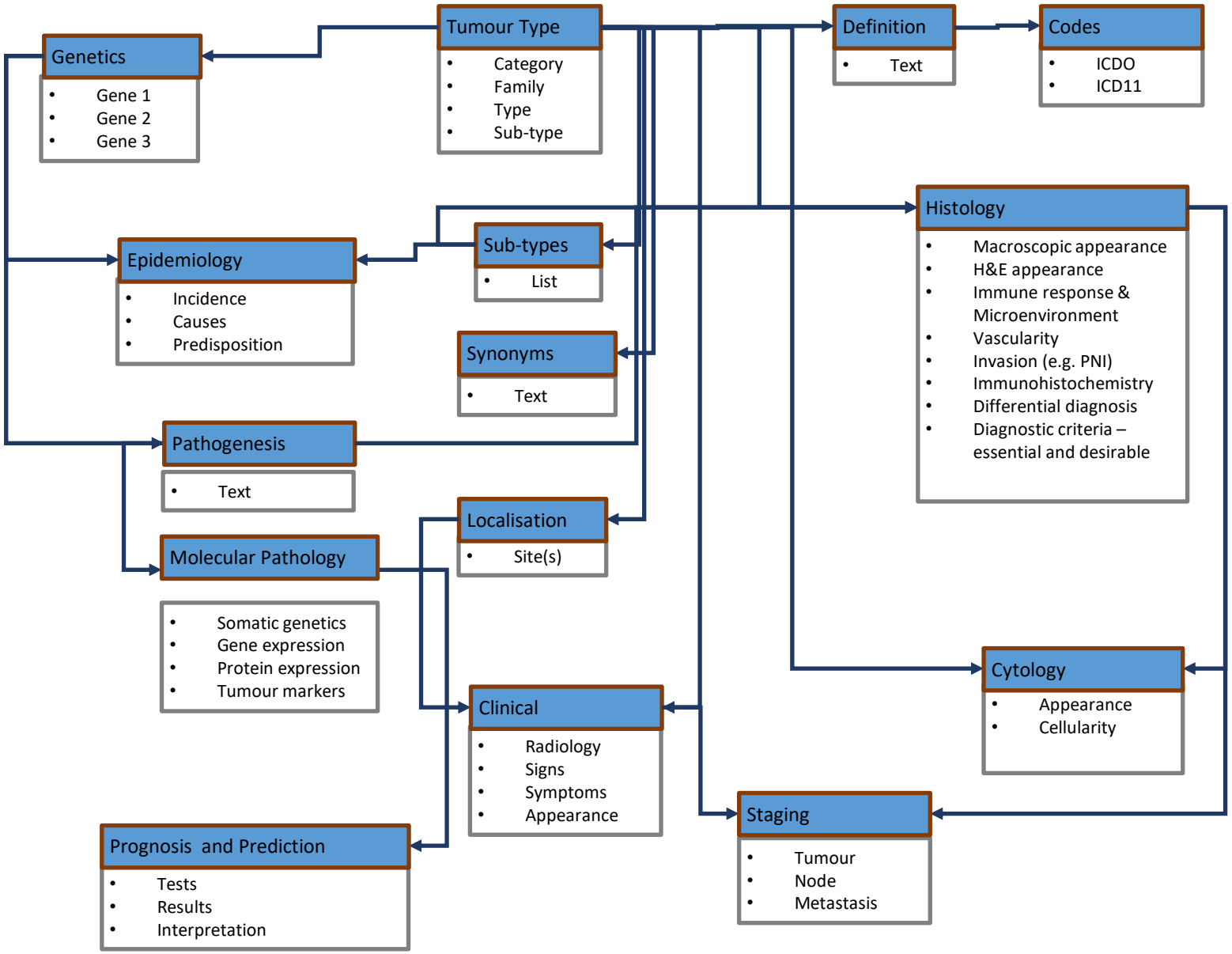

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- Subtypes
- Localization
- Clinical features and Radiology
- Epidemiology
- Etiology
  - Causes
  - Predisposing factors (Genetics)
- Pathogenesis
- Macroscopic appearance
- Histopathology
  - H&E appearance
  - Immune response & Microenvironment
  - Vascularity
  - Invasion (e.g. PNI)
  - Immunohistochemistry
  - Differential diagnosis
- Cytology
- Diagnostic 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
  - CGC genomics compendium
  - TNM (UICC)

Examples…

- Bile duct and gallbladder carcinomas

- Genetic Tumour Syndromes

Classification terms (2019)

- *Site*: Tumours of the gallbladder and extrahepatic bile ducts
- *Category*: Epithelial tumours
- *Family* (Class): Malignant epithelial tumours
- *Type:* Carcinoma of the gallbladder
- *Sub-Type* (Variant):
  - adenocarcinoma, intestinal type (8144/3);
  - clear cell adenocarcinoma NOS (8310/3);
  - mucinous cystic neoplasm with associated invasive carcinoma (8470/3);
  - mucinous adenocarcinoma (8480/3);
  - poorly cohesive carcinoma (8490/3);
  - intracystic papillary neoplasm with associated invasive carcinoma (8503/3)

Stage and Grade are dealt with separately….

WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1). https://publications.iarc.fr/579.

ICD-O 3.2 coding – anatomy

C22 LIVER AND INTRAHEPATIC BILE DUCTS		
C22.0 Liver		
C22.1 intrahepatic bile duct		
C23 GALLBLADDER		
C23.9 Gallbladder		
C24 OTHER AND UNSPECIFIED PARTS OF BILIARY TRACT		
C24.0 Extrahepatic bile duct		
C24.1 Ampulla of Vater		
C24.8 Overlapping lesion of billiary tract		
C24.9 Billiary tract, NOS		

ICD-O topographical coding for the anatomical sites (WCT - DIG5)

- C23 Gallbladder
  - C23.9 Gallbladder
- C24 Other and unspecified parts of the biliary tract
  - C24.0 Extrahepatic bile duct NOS
  - C24.1 Ampulla of Vater
  - **C24.2 Distal (extrahepatic) bile duct**
  - **C24.3 Perihilar (or proximal) bile duct**
  - **C24.4 Cystic duct**
  - C24.8 Overlapping lesion of the biliary tract
  - C24.9 Biliary tract NOS

WHO Classification of Tumours Online (1): tumourclassification.iarc.who.int

International Agency for Research on Cancer
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Digestive System Tumours (5th ed.) // Tumours of the liver and intrahepatic bile ducts // Epithelial tumours // Malignant biliary tumours // Intrahepatic cholangiocarcinoma

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Intrahepatic cholangiocarcinoma

Definition
Intrahepatic cholangiocarcinoma (iCCA) is a malignant intrahepatic epithelial neoplasm with biliary differentiation.

ICD-O coding
8160/3 Cholangiocarcinoma

ICD-11 coding
2C12.10 & XH7M15 Intrahepatic cholangiocarcinoma & Cholangiocarcinoma

Related terminology
Acceptable: intrahepatic bile duct carcinoma.
Not recommended: peripheral cholangiocarcinoma; cholangiocellular carcinoma; cholangiolocellular carcinoma.

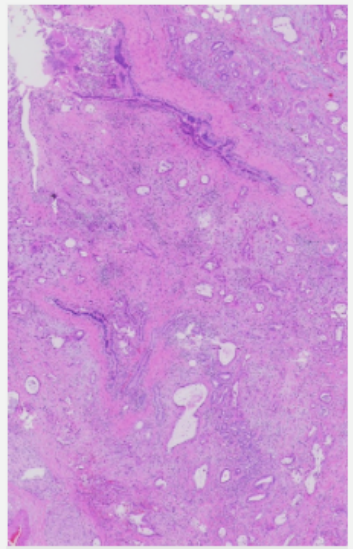
Subtype(s)
iCCA has two main subtypes: large duct and small duct. Large duct iCCA arises in the large intrahepatic bile ducts near the hepatic hilus (proximal to the right and left hepatic ducts) and resembles perihilar and extrahepatic cholangiocarcinoma. Small duct iCCA preferentially occurs in the hepatic periphery (see Table #0384) { 28338651 ; 25181580 ; 18393293 }. Cholangiolocarcinoma and iCCA with ductal plate malformation–like pattern are subtypes of small duct iCCA. Rare subtypes described in perihilar and extrahepatic cholangiocarcinoma can also occur in large duct iCCA (see Box #0385) { 21344355 ; 28126467 ; 23073321 }.

Localization
iCCA arises in the liver peripheral/proximal to the left and right hepatic ducts. Large duct iCCA is preferentially located closer to the liver hilum and primarily spreads along the large portal tracts with a periductal infiltrating (PI) pattern. Small duct iCCA is mainly located in the peripheral parts of the liver and primarily shows a mass-forming (MF) pattern.

Clinical features
The average age at diagnosis is > 50 years, with a peak incidence between the fifth and seventh decades of life, and there is a slight male predominance. CA19-9 is typically elevated. General malaise, abdominal pain, and weight loss are frequent symptoms. Large duct iCCAs (PI pattern) with central bile duct obstruction may present with cholestasis or cholangitis. Small duct iCCA (MF pattern) often goes unnoticed until it reaches a relatively large size.

Epidemiology
iCCA is the second most common primary hepatic malignancy next to hepatocellular carcinoma and accounts for about 10–15% of primary liver cancers { 25204668 }. The incidence of iCCA is increasing in many geographical areas { 27000463 }. It is highest in south-eastern Asia (as many as 71.3 cases per 100 000 person-years), especially in Thailand (> 80 cases per 100 000 person-years), and lower in Europe (0.2–1.8 cases per 100 000 person-years). In the USA, the incidence increased from 0.92 cases per 100 000 person-years in 1995–2004 to 1.09 cases per 100 000 person-years in 2005–2014 { 29469047 }.

View tables and boxes



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Digestive System Tumours
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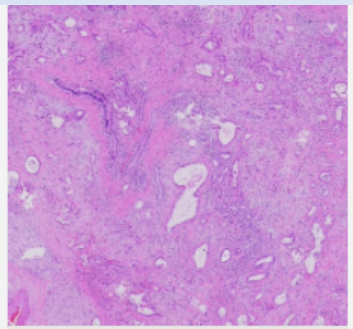

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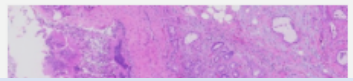

ICD-O coding
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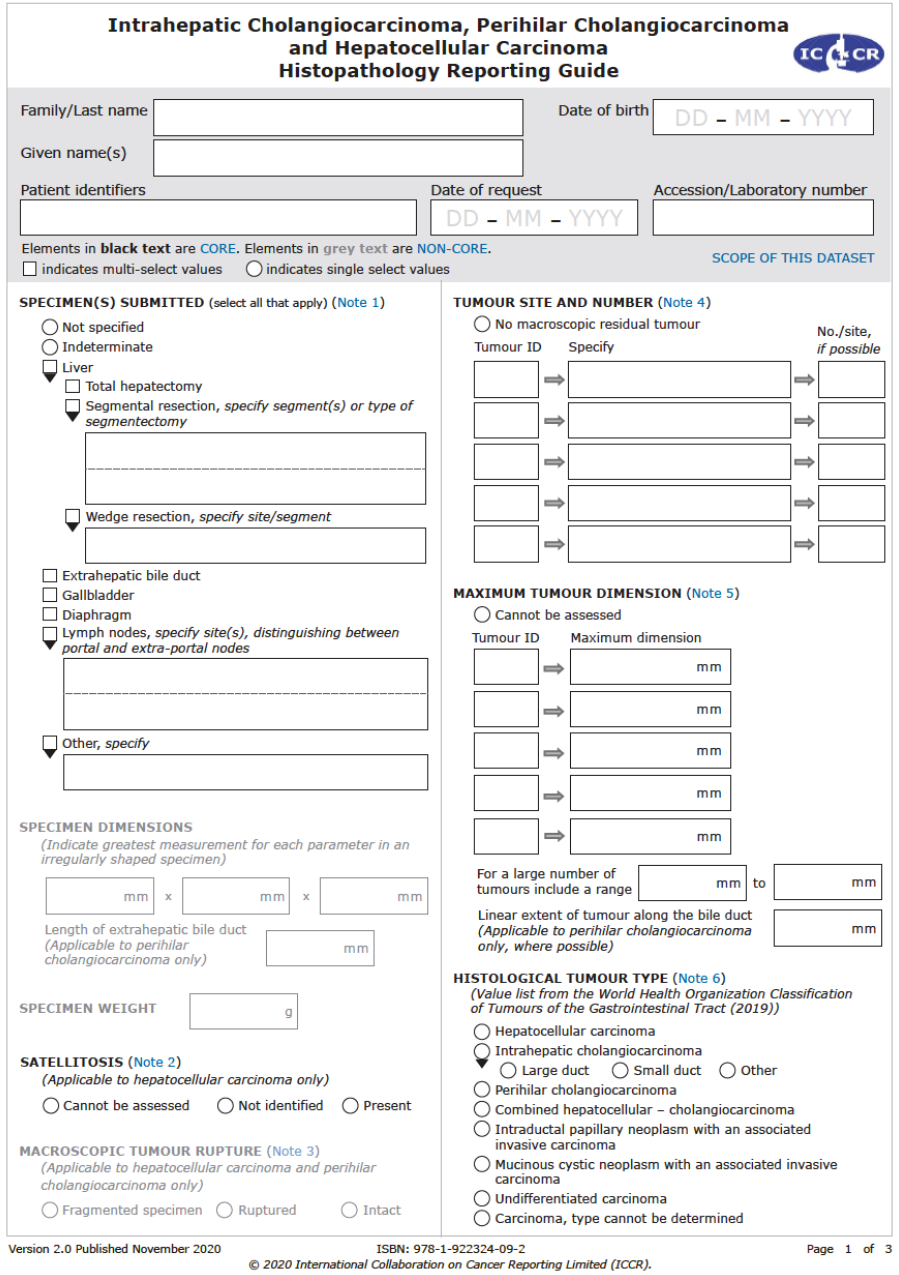
Tumours of the gallbladder and extrahepatic bile ducts

- **Epithelial tumours**
  - *Benign epithelial tumours and precursors*
    - Pyloric gland adenoma of the gallbladder
    - Biliary intraepithelial neoplasia
    - Intracholecystic papillary neoplasm (formerly Intracystic / intraductal papillary neoplasm)
    - Intraductal papillary neoplasm of the bile ducts
  - ***Malignant epithelial tumours***
    - Carcinoma of the gallbladder
    - Carcinoma of the extrahepatic bile ducts
    - Neuroendocrine neoplasms of the gallbladder and bile ducts

International reporting guidance

- Guidance can differ between countries – driven by many factors
- The International Collaboration for Cancer Reporting (ICCR) seeks to provide international standards – http://www.iccr-cancer.org/datasets
- https://www.iccr-cancer.org/datasets/published-datasets/digestive-tract/liver/ for Intrahepatic Cholangiocarcinoma, Perihilar Cholangiocarcinoma and Hepatocellular Carcinoma



Intrahepatic Cholangiocarcinoma, Perihilar Cholangiocarcinoma and Hepatocellular Carcinoma
Histopathology Reporting Guide

Family/Last name | Date of birth DD – MM – YYYY
Given name(s)
Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are CORE. Elements in grey text are NON-CORE.
☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

SPECIMEN(S) SUBMITTED (select all that apply) (Note 1)
◯ Not specified
◯ Indeterminate
☐ Liver
  ☐ Total hepatectomy
  ☐ Segmental resection, *specify segment(s) or type of segmentectomy*
  ☐ Wedge resection, *specify site/segment*
☐ Extrahepatic bile duct
☐ Gallbladder
☐ Diaphragm
☐ Lymph nodes, *specify site(s), distinguishing between portal and extra-portal nodes*
☐ Other, *specify*

SPECIMEN DIMENSIONS
(Indicate greatest measurement for each parameter in an irregularly shaped specimen)
mm x mm x mm
Length of extrahepatic bile duct *(Applicable to perihilar cholangiocarcinoma only)* mm

SPECIMEN WEIGHT g

SATELLITOSIS (Note 2)
(Applicable to hepatocellular carcinoma only)
◯ Cannot be assessed ◯ Not identified ◯ Present

MACROSCOPIC TUMOUR RUPTURE (Note 3)
(Applicable to hepatocellular carcinoma and perihilar cholangiocarcinoma only)
◯ Fragmented specimen ◯ Ruptured ◯ Intact

TUMOUR SITE AND NUMBER (Note 4)
◯ No macroscopic residual tumour

Tumour ID	Specify	No./site, *if possible*

MAXIMUM TUMOUR DIMENSION (Note 5)
◯ Cannot be assessed

Tumour ID	Maximum dimension
	mm
	mm
	mm
	mm
	mm

For a large number of tumours include a range mm to mm
Linear extent of tumour along the bile duct *(Applicable to perihilar cholangiocarcinoma only, where possible)* mm

HISTOLOGICAL TUMOUR TYPE (Note 6)
(Value list from the World Health Organization Classification of Tumours of the Gastrointestinal Tract (2019))
◯ Hepatocellular carcinoma
◯ Intrahepatic cholangiocarcinoma
  ◯ Large duct ◯ Small duct ◯ Other
◯ Perihilar cholangiocarcinoma
◯ Combined hepatocellular – cholangiocarcinoma
◯ Intraductal papillary neoplasm with an associated invasive carcinoma
◯ Mucinous cystic neoplasm with an associated invasive carcinoma
◯ Undifferentiated carcinoma
◯ Carcinoma, type cannot be determined

Version 2.0 Published November 2020 ISBN: 978-1-922324-09-2

Examples…

- Bile duct and gallbladder carcinomas

- Genetic Tumour Syndromes

Inception of the genetic tumour syndromes volume

- Session at the 2019 European Congress of Pathology in Nice, France.
- Discussion in the WHO Classification of Tumours editorial board.
- Taxonomies are hierarchical systems, and ideally have multiple options under each level.
- In some GTS, there can be fairly direct 1:1 correlations between *cellular mechanisms, molecular pathways*, *syndromes* and *genes.*
- Inevitably, there are some syndromes that involve the same genes, but have different names or expressions of the disease depending on the DNA alteration present or their ability to affect multiple pathways.

Organization of GTS5

1. *Category:* cellular mechanism – e.g. DNA repair
2. *Family:* molecular pathway – e.g. mismatch repair
3. *Type:* syndrome name, e.g. Lynch syndrome, as used in practice as a diagnostic entity
4. *Subtype:* Gene – *MLH1*; *PMS2*; *MSH2; MSH6*

Classification - mechanisms

1. Growth factor receptors and related signalling pathways
2. Oxidative stress response and metabolism
3. Cell cycle and apoptosis pathways
4. DNA repair and genomic stability
5. Telomere maintenance
6. Epigenetic drivers and chromatin remodelling
7. RNA regulation
8. Protein regulation

WHO Classification of Tumours Online (1): tumourclassification.iarc.who.int

International Agency for Research on Cancer
World Health Organization

WHO Classification of Tumours online

Genetic Tumour Syndromes (5th ed.) //Cell cycle and apoptosis pathways //RB pathway //Retinoblastoma syndrome (*RB1*)

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Retinoblastoma syndrome (*RB1*)

Definition

Retinoblastoma (RB) syndrome is an autosomal dominant cancer predisposition syndrome linked to a germline *RB1* heterozygous pathogenic variant and development of retinoblastoma as well as other extraocular primary malignancies.

ICD-O coding

MIM numbering
180200 Retinoblastoma; RB1

ICD-11 coding

2D02.2 Retinoblastoma

Related terminology

Acceptable: heritable retinoblastoma; familial retinoblastoma.

Subtype(s)

Heritable unilateral and bilateral retinoblastoma;
Trilateral retinoblastoma – bilateral with primary intracranial tumour (pineal or suprasellar tumour);
Non-ocular second primary malignancies (SPM).

Localization

Retinoblastoma develops in the retina of one or both eyes. In the retinoblastoma syndrome, bilateral tumours usually occur and present as multicentric retinal tumours. In about 15% of patients the syndrome is associated with unilateral disease, thus the need for molecular test for *RB1* and not to rely on a clinical diagnosis solely { 29056300 }. Synchronous or metachronous involvement by malignant intracranial pineal or suprasellar tumours may develop in about 3.5% of these children. Co-occurrence of intracranial malignant tumours and retinoblastoma is referred to as trilateral retinoblastoma { 29056300 }. In contrast to intraocular retinoblastoma, which has excellent cure rate if treated prior to extraocular spread { 24589388 ; 25126964 }, pineoblastoma is low and mostly fatal and surveillance is critical { 24589388 ; 25126964 }. Patients may develop SPM starting in their second or third decades of life with overall risk of 0.5-1% per year of life { 9727521 }. The most frequent secondary malignancies are rhabdomyosarcoma, osteosarcoma, other soft tissue sarcomas, endometrial adenocarcinoma, lung carcinoma and skin melanoma { 25185089 ; 31622129 }.

Clinical features

A white pupillary reflex (leukocoria) is the most common presentation (63% of cases) for intraocular retinoblastoma and results from the retinal tumour { 32105305 }. Strabismus is the second most common presentation (10% of cases) followed by the combination of leukocoria and strabismus { 34592118 }. In advanced retinoblastoma, there may be iris heterochromia (neovascularization of iris), glaucoma with buphthalmos, pseudohypopyon, hyphema and aseptic orbital cellulitis { 26023180 }. In tumours with extraocular manifestations, extension proptosis or a cauliflower-like mass arising from the front of the eye may be present. Proptosis presentation is more common in low- and middle income countries (LMIC) compared to high-income countries. Children from LMICs are older at presentation, with more advanced disease and less percentage of familial retinoblastoma, probably secondary to not reaching childbearing age, however, more studies are necessary to ascertain the

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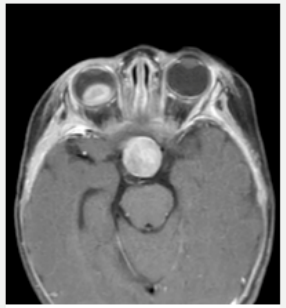
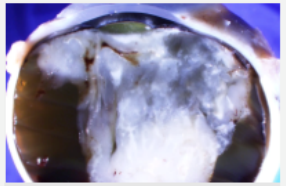


#37653
MRI of trilateral retinoblastoma



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Definition
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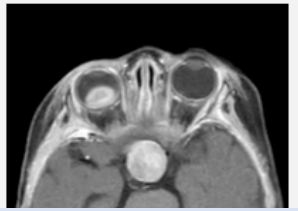


Genetic Tumour Syndromes
/ Cell cycle and apoptosis pathways
// RB pathway
/// Retinoblastoma syndrome

1. Growth factor receptors and related signalling pathways

Growth factor receptors
- Hereditary papillary renal carcinoma
- Multiple endocrine neoplasia type 2
- Juvenile polyposis syndrome
- Hereditary neuroblastoma
- Encephalocraniocutaneous lipomatosis

G-coupled protein receptor pathway
- Glucagon cell hyperplasia and neoplasia
- McCune-Albright syndrome
- Sturge-Weber syndrome

RAS-MAPK pathway
- Neurofibromatosis type 1
- NF2-related schwannomatosis
- Costello syndrome
- Noonan syndrome
- Schimmelpenning-Feuerstein-Mims

PKA signalling pathway
- Carney complex
- PROS syndrome

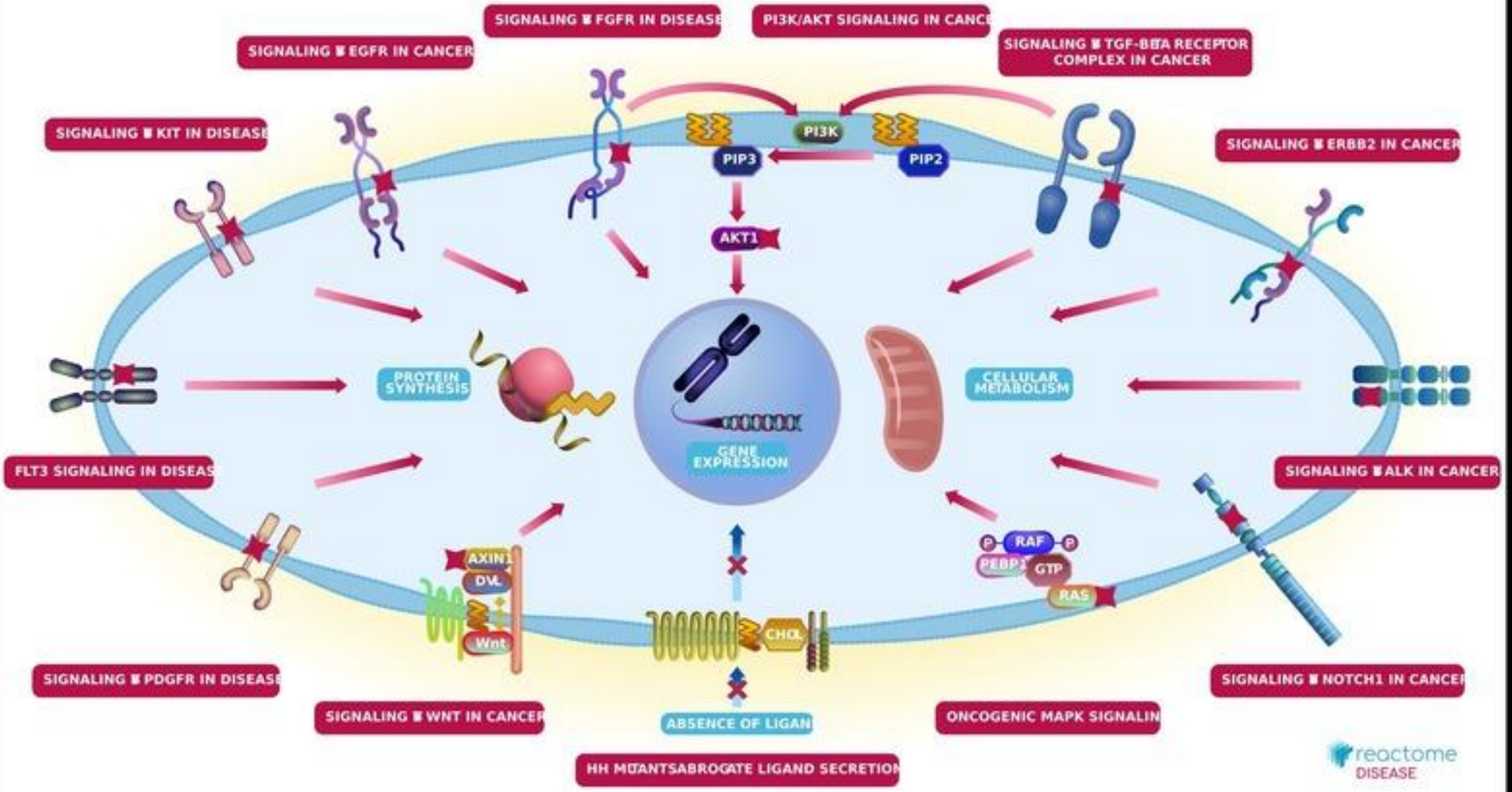
WNT/TGFbeta pathway
- Familial adenomatous polyposis
- 1Gastric Adenocarcinoma and Proximal Polyposis of Stomach (GAPPS)
- AXIN2-associated polyposis
- Serrated polyposis
- WT1 related tumour predisposition syndrome
- WAGR syndrome
- Multiple endocrine neoplasia type 1
- Peutz-Jeghers syndrome
- Hereditary gastric and breast cancer syndrome
- Hereditary mixed polyposis syndrome

Hedgehog signalling pathway
- Naevoid basal cell carcinoma syndrome (Gorlin syndrome)
- SMO-related Curry-Jones syndrome
- ELP1-related medulloblastoma predisposition syndrome
- Osteochondromatosis

NF-kB signalling pathway
- Brooke-Spiegler syndrome

MTOR and PI3K pathway
- Tuberous sclerosis
- PTEN hamartoma tumour syndrome
- Activated Phosphatidylinositol-3-OH kinase δ Syndrome (APDS)

Transcription factors and regulators
- Multiple endocrine neoplasia type 5 (MAX related tumours)
- MAFA-related familial insulinomatosis
- Birt-Hogg-Dube syndrome
- Familial chordoma
- Hyperparathyroidism jaw tumour syndrome (CDC73)


SIGNALING IN FGFR IN DISEASE
PI3K/AKT SIGNALING IN CANCE
SIGNALING IN EGFR IN CANCER
SIGNALING IN TGF-BETA RECEPTOR COMPLEX IN CANCER
SIGNALING IN KIT IN DISEASE
PI3K
PIP3
PIP2
SIGNALING IN ERBB2 IN CANCER
AKT1
PROTEIN SYNTHESIS
CELLULAR METABOLISM
GENE EXPRESSION
FLT3 SIGNALING IN DISEAS
SIGNALING IN ALK IN CANCER
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ABSENCE OF LIGAN
ONCOGENIC MAPK SIGNALIN
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HH MUTANTS ABROGATE LIGAND SECRETION
reactome
DISEASE

2. Oxidative stress response and metabolism

Angiogenesis

- Von Hippel-Lindau syndrome (VHL)

Krebs cycle

- SDH-deficient tumour syndrome - Hereditary phaeochromocytoma-paraganglioma syndromes (SDHA, SDHB, SDHC, SDHD, SDHAF2)
- Hereditary leiomyomatosis and renal cell carcinoma syndrome (FH)

Toxic metabolite-mediated disorders

- Hereditary tyrosinaemia type 1 (FAH)

3. Cell cycle and apoptosis pathways

P53 pathway

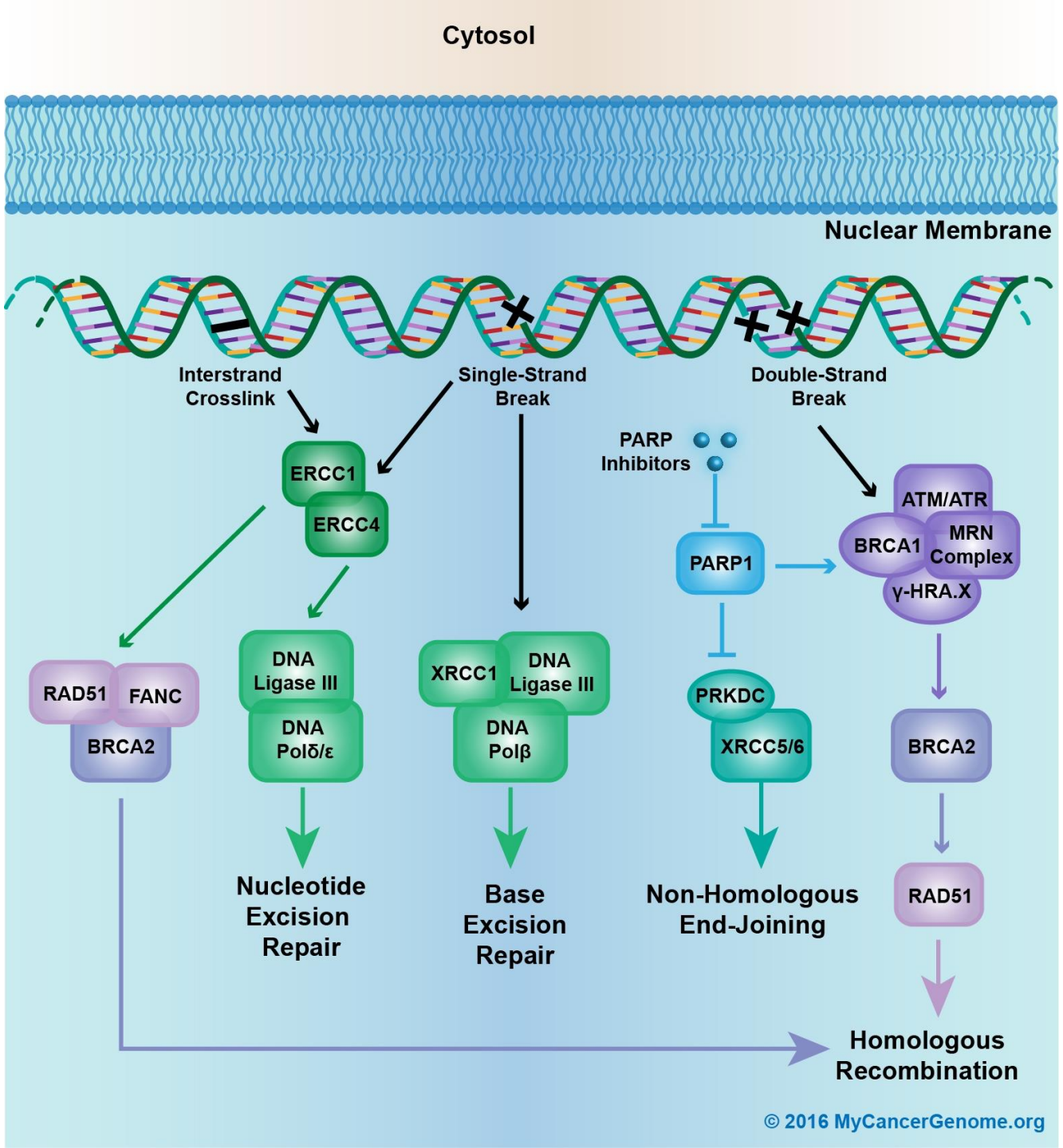
- Li-Fraumeni syndrome (TP53)

RB pathway

- Retinoblastoma syndrome (RB1)
- Multiple endocrine neoplasia type 4 (CDKN1B)
- CDKN2A-related tumour predisposition syndrome (CDKN2A)
- CDK4-related melanoma predisposition syndrome (CDK4)

- **FAS pathway**
  - Autoimmune lymphoproliferative syndrome (FAS)

DNA repair pathways



4. DNA repair and genomic stability

Mismatch repair

- Lynch Syndrome (MLH1, PMS2, MSH2, MSH6)
- Muir-Torre syndrome (MLH1, PMS2, MSH2, MSH6)
- Constitutional mismatch repair deficiency (CMMRD) syndrome (MLH1, PMS2, MSH2, MSH6)

Homologous recombination

- BRCA-related cancer predisposition syndrome (BRCA1, BRCA2)
- PALB2-related cancer predisposition syndrome (PALB2)
- RAD51-related cancer predisposition syndrome (RAD51C, RAD51D)
- Fanconi anaemia (FANC genes)

Base excision repair genes

- MUTYH-associated polyposis (MUTYH)
- NTHL1-related tumour syndrome (NTHL1)
- MBD4-associated neoplasia syndrome (MBD4)

Deficient nucleotide excision repair (NER) of DNA damage

- Xeroderma Pigmentosum

Non-homologous end joining (NHEJ)

- Ataxia-telangiectasia syndrome (ATM)
- CHEK2-related hereditary (breast) cancer predisposition syndrome (CHEK2)
- Nijmegen breakage syndrome (NBN)

DNA Polymerization

- Polymerase proofreading-associated polyposis (POLD1, POLE)

Helicases

- Bloom syndrome (BLM)
- Werner syndrome (WRN)
- Rothmund-Thomson syndrome (ANAPC1, RECQL4)
- DDX41-related haematologic tumour predisposition syndrome (DDX41)

Chromosomal non-dysjunction (aneuploidy) syndromes

- Mosaic variegated aneuploidy (BUB1B, CEP57, TRIP13, BUB1, BUB3)
- Klinefelter syndrome
- Turner syndrome
- Down syndrome

5. Telomere maintenance

Telomere biology disorders

- Dyskeratosis congenita (DKC1, TERT, TERC, TINF2, Other IBMFS genes)
- POT1 and Shelterin-related tumour predisposition syndrome (POT1, ACD, TERF2IP, TERT promoter)

6. Epigenetic drivers and chromatin remodelling

Imprinting disorders

- Beckwith-Wiedemann spectrum (IGF2; CDKN1C)

Histone and DNA methylation

- Enchondromatosis (IDH1, IDH2)

Chromatin remodelling pathway

- Rhabdoid tumour predisposition syndrome (SMARCB1, SMARCA4)
- Schwannomatosis (SMARCB1, LZTR1)
- Clear cell meningioma predisposition syndrome (SMARCE1)
- Weaver syndrome (EZH2)

7. RNA regulation

MicroRNA

- DICER1-related tumour predisposition syndrome (DICER1)
- MicroRNA processor tumour predisposition syndromes (DROSHA, DGCR8)

RNA splicing

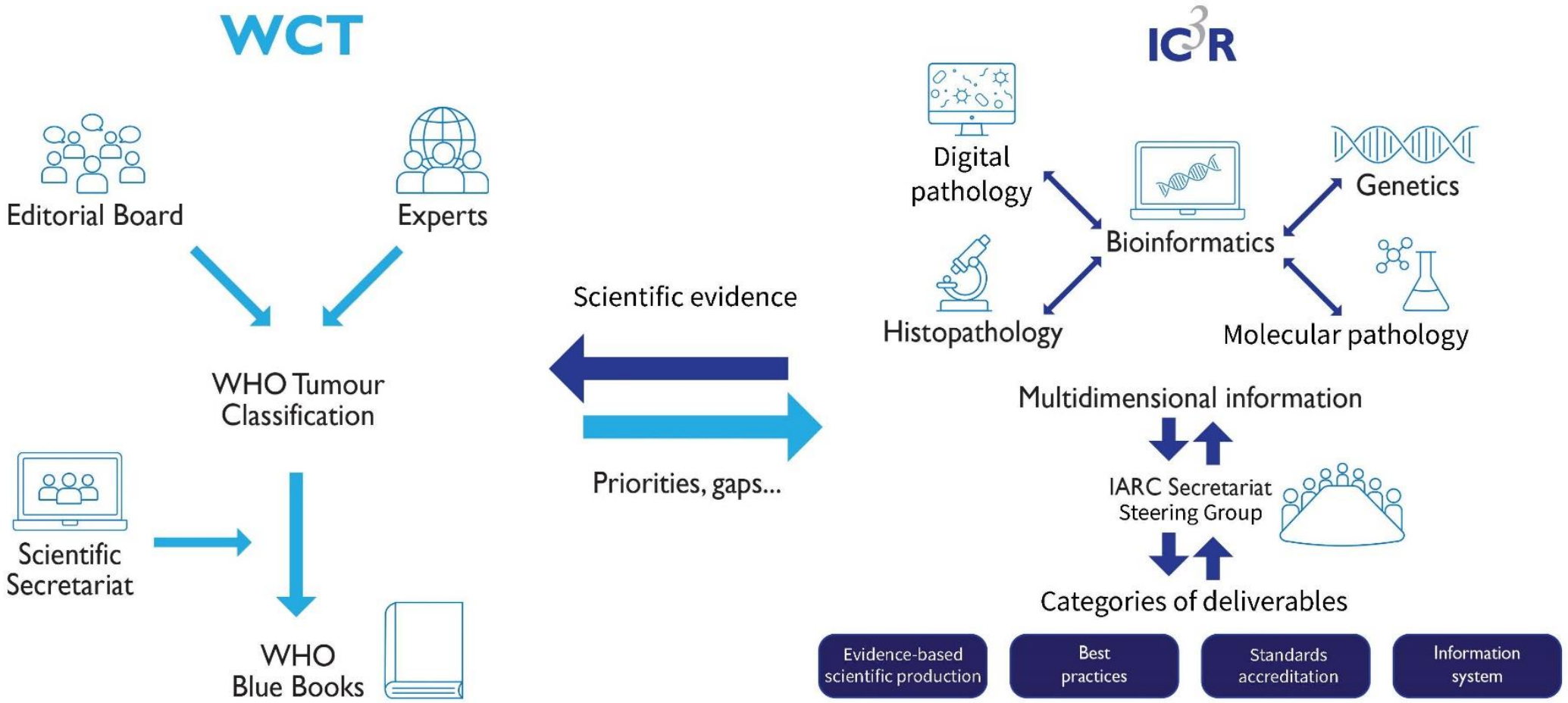
- Goldenhar syndrome (MYT1, SF3B2)

8. Protein regulation

Ubiquitin pathway

- BAP1-related tumour predisposition syndrome (BAP1)

The WHO Classification of Tumours (WCT) and the IARC International Collaboration for Cancer Classification and Research



Vision

An online open, easily accessible tool which allows users to explore evidence published informative for the WCT and easily detect gaps and pockets of low level evidence.

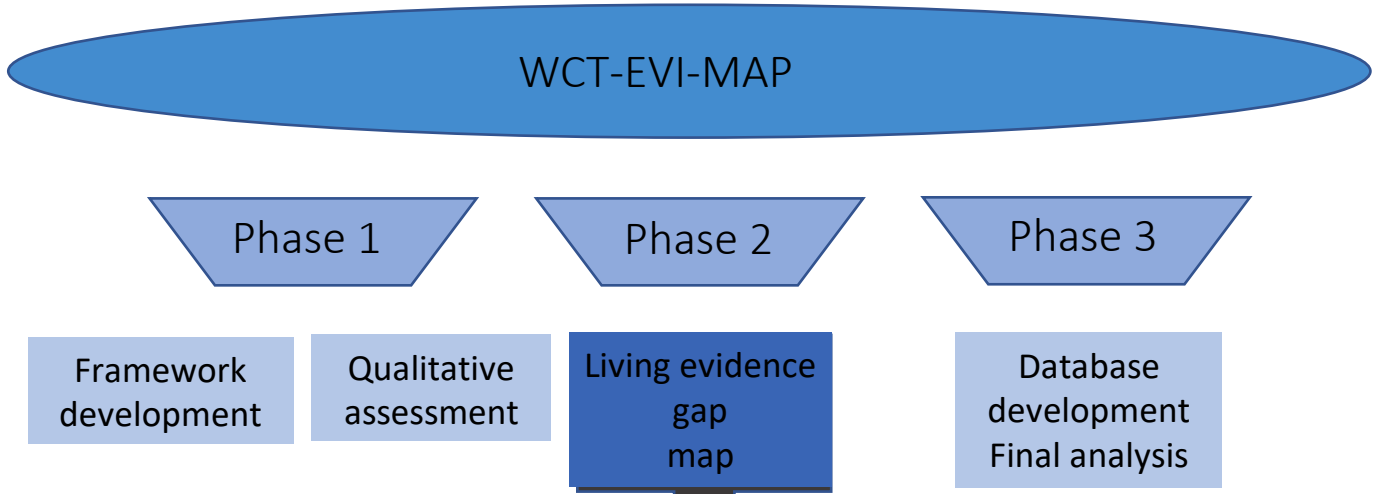
Goals

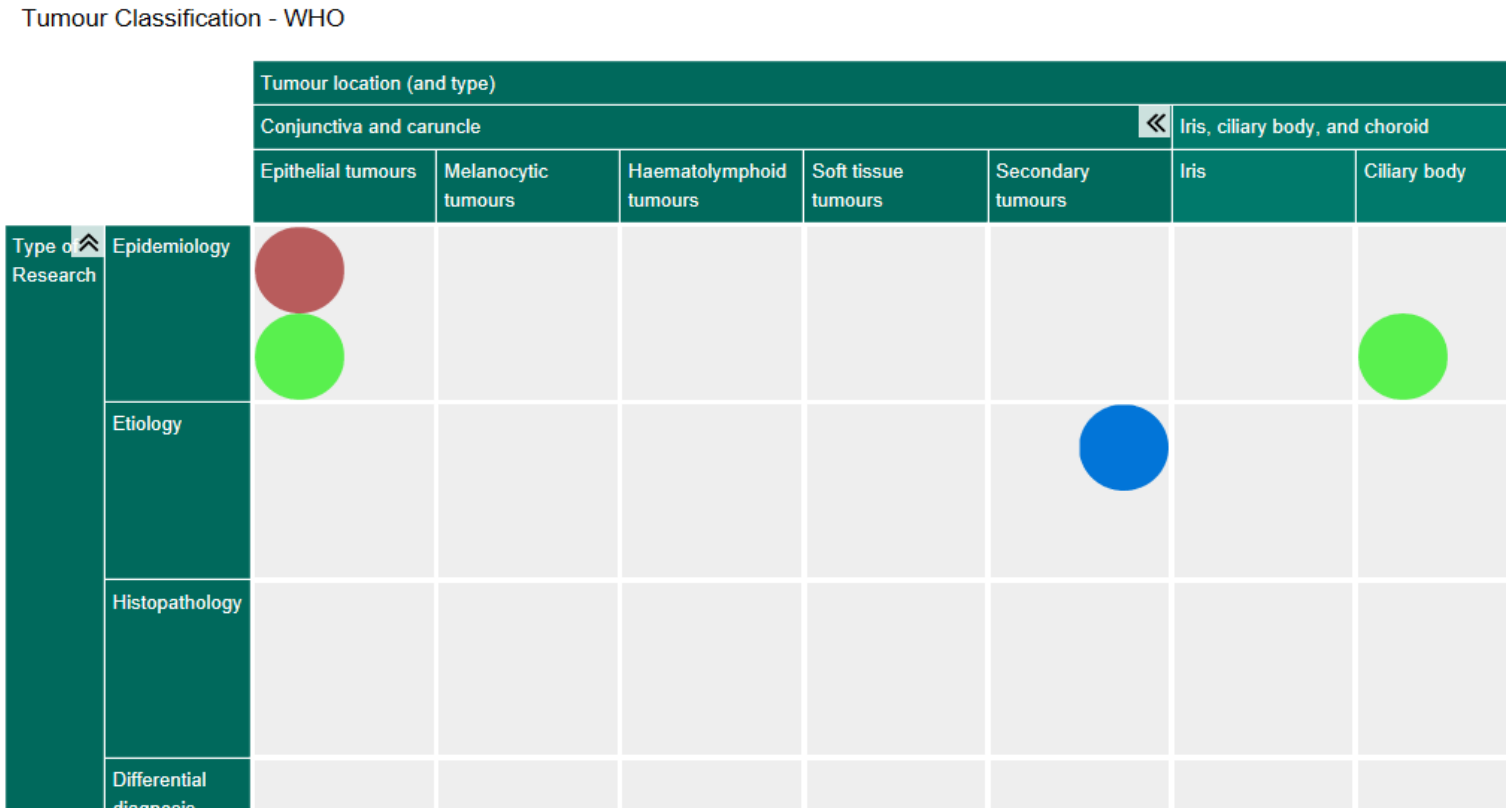
To map available evidence for the whole WCT with a living approach.

Strategies

A mixed method and step wise approach:

(A) development of the framework
(B) definition of dimensions and assessment of usability
(C) evidence-gap mapping of the WCT
(D) set up of the relational data base of evidence maps and dissemination of results
(E) final analysis





WCT topics:	Etiology		Clinical features Radiology Localisation Macroscopy, Histopathology Immunohistochemistry Cytology	Diagnostic molecular pathology Diagnostic immunohistochemistry	Prognosis Staging	Prediction
	Epidemiology Prevalence Incidence Risk factors	Mechanisms & Pathogenesis				
Research focus:	Population	Cellular, molecular & genetic biology	Pathological characterisation and diagnosis of the tumor	Diagnostic tests (accuracy) and reproducibility (precision)	Prognostics	Predictive biomarkers
Clinical questions:	How common is this tumour? What factors influence the probability of developing this tumour? Who is at risk?	What are the molecular alterations in this tumor? What mechanisms cause this tumor?	What are the key features of this tumor? How to we define the tumor?	How well does this test confirm the diagnosis?	What features influence five-year survival?	Can this marker predict treatment?
Level 1	*Systematic reviews**	*Systematic reviews**	*Systematic reviews**	*Systematic reviews**	*Systematic reviews**	*Systematic reviews**
Level 2	*Cancer registry data* *Prospective cohort studies* *Randomised-controlled trials*	*Prospective cohort studies* *Studies derived from randomised-controlled trials*	*Case-control studies* *Diagnostic test accuracy studies* *Diagnostic agreement/reproducibility studies* *Prospective cohort studies* *Studies derived from randomised-controlled trials*	*Case-control studies* *Diagnostic test accuracy studies* *Diagnostic agreement/reproducibility studies* *Prospective cohort studies* *Studies derived from randomised-controlled trials* *Randomised-controlled trials of diagnostic tests*	*Prospective Cohort studies* *Studies derived from randomised-controlled trials*	*Randomised-controlled trials* *Prospective Cohort studies* *Studies derived from randomised-controlled trials*
Level 3	*Case-control studies* *Retrospective cohort studies* *Other cross-sectional studies*	*Case-control studies* *Mechanistic clinical studies* *Other cross-sectional studies* *Retrospective cohort studies*	*Consensus studies* *Other cross-sectional studies* *Retrospective cohort studies*	*Case series* *Consensus studies* *Retrospective cohort studies* *Other cross-sectional studies*	*Case-control studies* *Retrospective Cohort studies* *Observational trials* *Other cross-sectional studies*	*Case-control studies* *Retrospective Cohort studies*
Level 4	*Case series*	*Animal studies* *Case series* *Mechanistic laboratory studies* *Molecular database entries* *Observational trials*	*Case series*	*Clinical laboratory test validation studies*	*Cancer registry data* *Diagnostic accuracy studies*	*Diagnostic accuracy studies*
Level 5	*Case reports*	*Case reports*	*Case reports*	*Not used*	*Case reports* *Case series*	*Case series* *Case reports* *Mechanistic clinical studies*

Conclusions

- The hierarchical WHO classification of tumours underpins the diagnosis of all tumours, worldwide.
- Diagnosis is not just made by histopathology - molecular pathology, endoscopy, radiology, blood markers and other technologies all play a role.
- Each discipline views the classification a different way: it is a multidimensional problem and the use of a database to systematise the characteristics of each tumour type has been transformative.
- The classification highlights the need for research and levels of evidence for future editions.
- 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

Thank you