



# The future of cancer classification

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International Agency for Research on Cancer



# 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.

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.**

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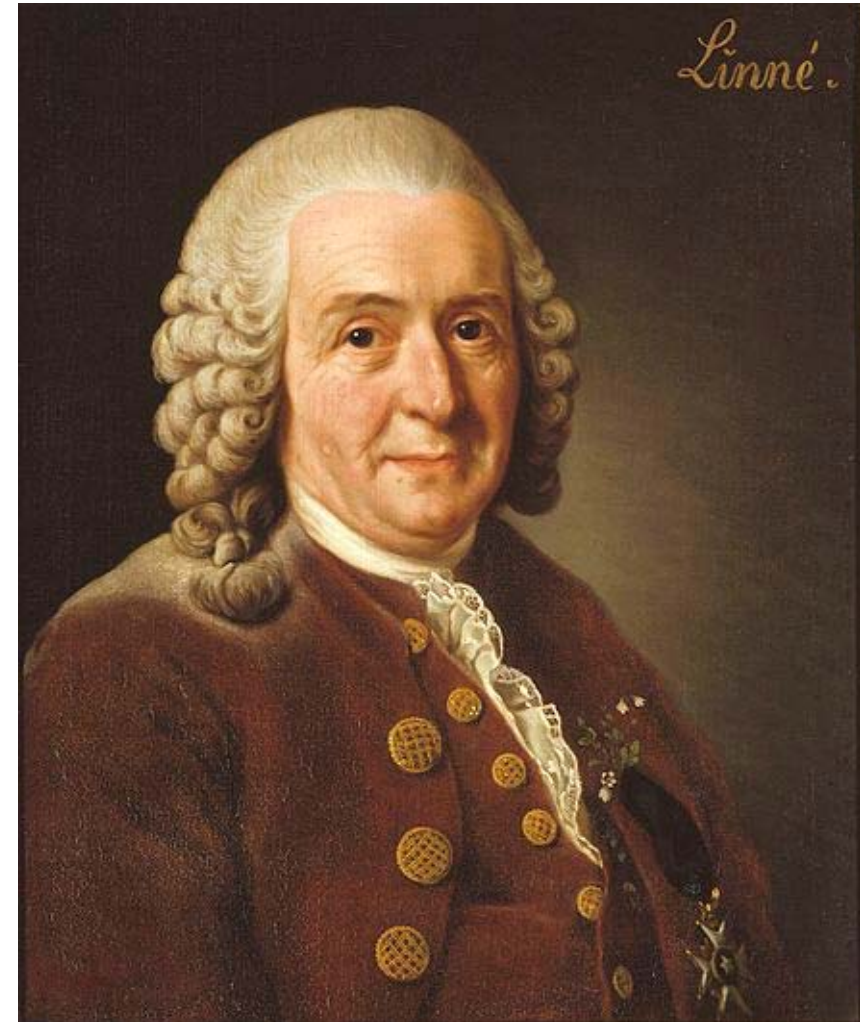
EDITIO DECIMA, REFORMATA.

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*Cum Privilegio S:æ R:æ M:tis Sveciæ.*

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**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)*

# WHO Blue Books

Scientific evidence



Illustrative cases



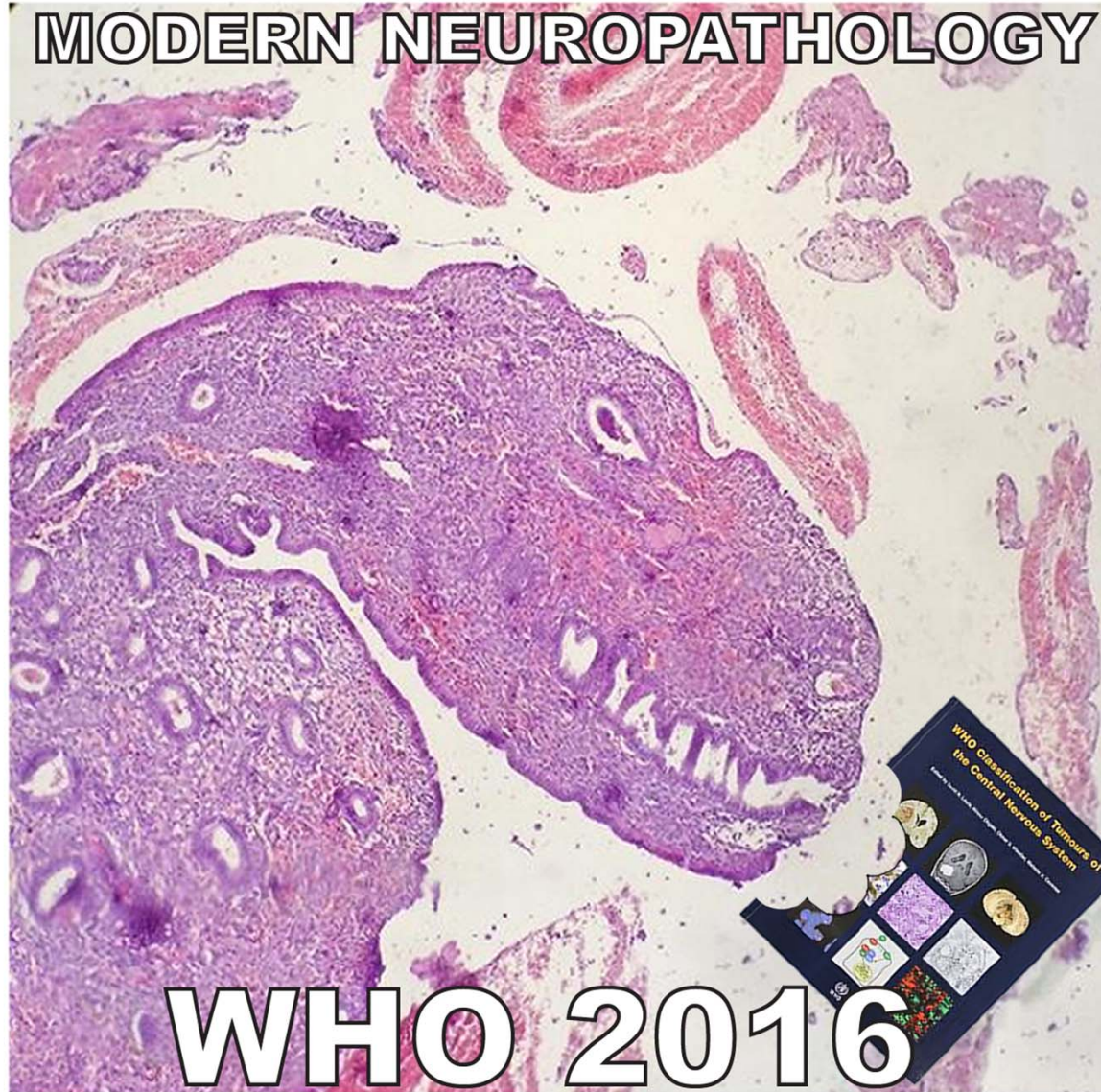
Diagnostic criteria



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# MODERN NEUROPATHOLOGY



# WHO 2016

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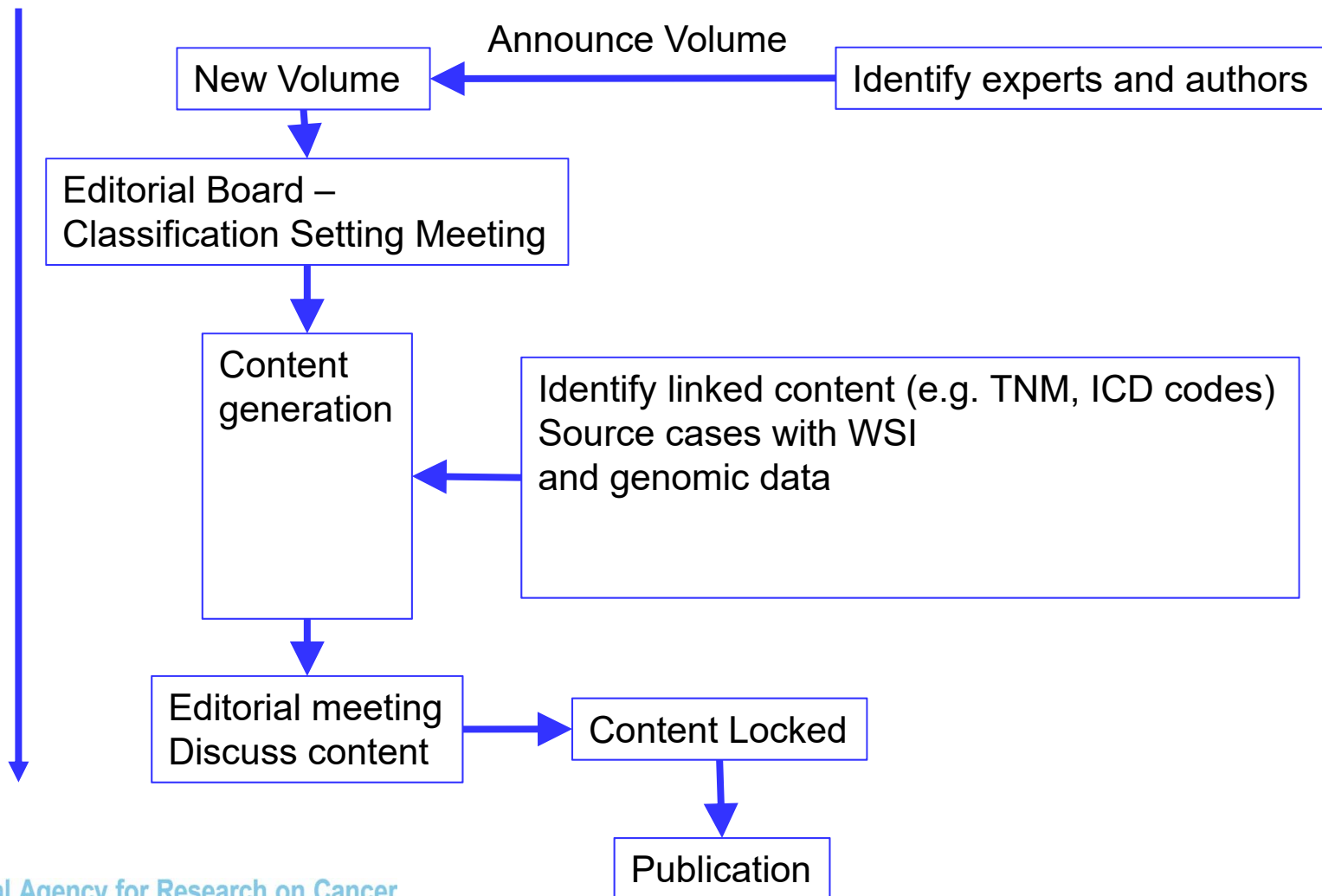


Slide courtesy of Dr Nada Jadabo

# 5<sup>th</sup> Series Changes

- Increased speed of production by improved process management at every stage
- Evidence not eminence...author selection by informed bibliometrics
- Editorial board formed with standing and expert members to consider and decide on classification, based on evidence – including systematic reviews
- Quality – HGVS for genomic notation, SI units (mm<sup>2</sup> not HPF)
- Epidemiology – from GICR epidemiologists
- Etiology, pathogenesis – incorporate new information - e.g. metabolites, genetic predisposition
- Harmonise topics across series – e.g. NEN, Lymph, ST&B
- Website to come, but there will still be books, and they will be blue!

## WHO Blue Books – 5<sup>th</sup> Series Timeline

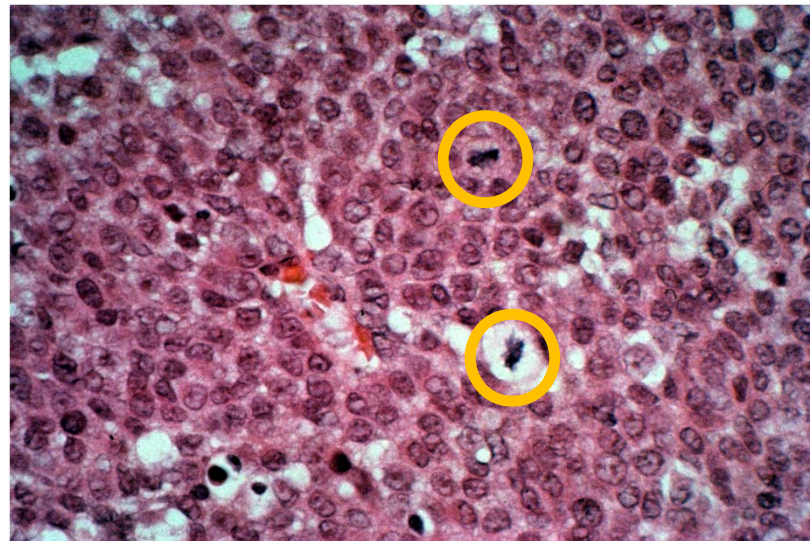


# *Improving quality*

- Why should research have lower standards than we would accept in clinical practice?
- New drug approvals require two independent and confirmatory phase 3 clinical trials (usually).
- What does pathological diagnosis need?
- Levels of evidence (summary):
  1. Systematic review
  2. Two independent prospective studies
  3. Two independent cohort studies of sufficient size
  4. Case reports, small cohort studies
  5. Expert opinion

# *Current challenge - Quality*

- Mitotic counts required for diagnosis to assess malignancy of many tumour types
- Usually expressed as 'mitoses per high power field (HPF)'
- But – HPF area varies with microscope and defined objective by a factor of 4x
- Why not use 'mitoses per mm<sup>2</sup>'?



## *Current challenge - Quality*

- HGVS notation mandatory for reporting of genetic alterations.
- Not understood by pathologists and largely ignored.
- Clinical colleagues may be told that there is a c. BRAF c.1799T>A (p.V600E) mutation in a melanoma....
- And then ask whether the 'BRAF is positive or negative'

<b>BRAF</b>	BRAF c.1799T>A p.Val600Glu	V600E
	BRAF c.1798_1799GT>AA p.Val600Glu	V600E
	BRAF c.1798_1799GT>AG p.Val600Arg	V600R
	BRAF c.1799_1800TG>AT p.Val600Asp	V600K

Kikuchi H, et al. Development and validation of a TaqMan Array for cancer mutation analysis. Pathogenesis. 2016 (3): 1–8.

## *Current challenge - Evidence*

- Changes in clinical practice are brought about by the weight of clinical evidence for and against.
- This involves assessment of the quality of the evidence
- Clinical evidence of efficacy relies on the dissemination of research results, usually by publication in medical journals – a critical step.
- Contopoulos-Ioannidis et al (2008) identified 101 articles between 1979-1983 in 6 top basic science journals that had apparent promise for development as a major clinical application. Twenty years later, only five of these promising advances were in licensed clinical use and only one of them had had a major impact on current medical practice.
- Clearly, the research system has not been working as effectively as one might wish.

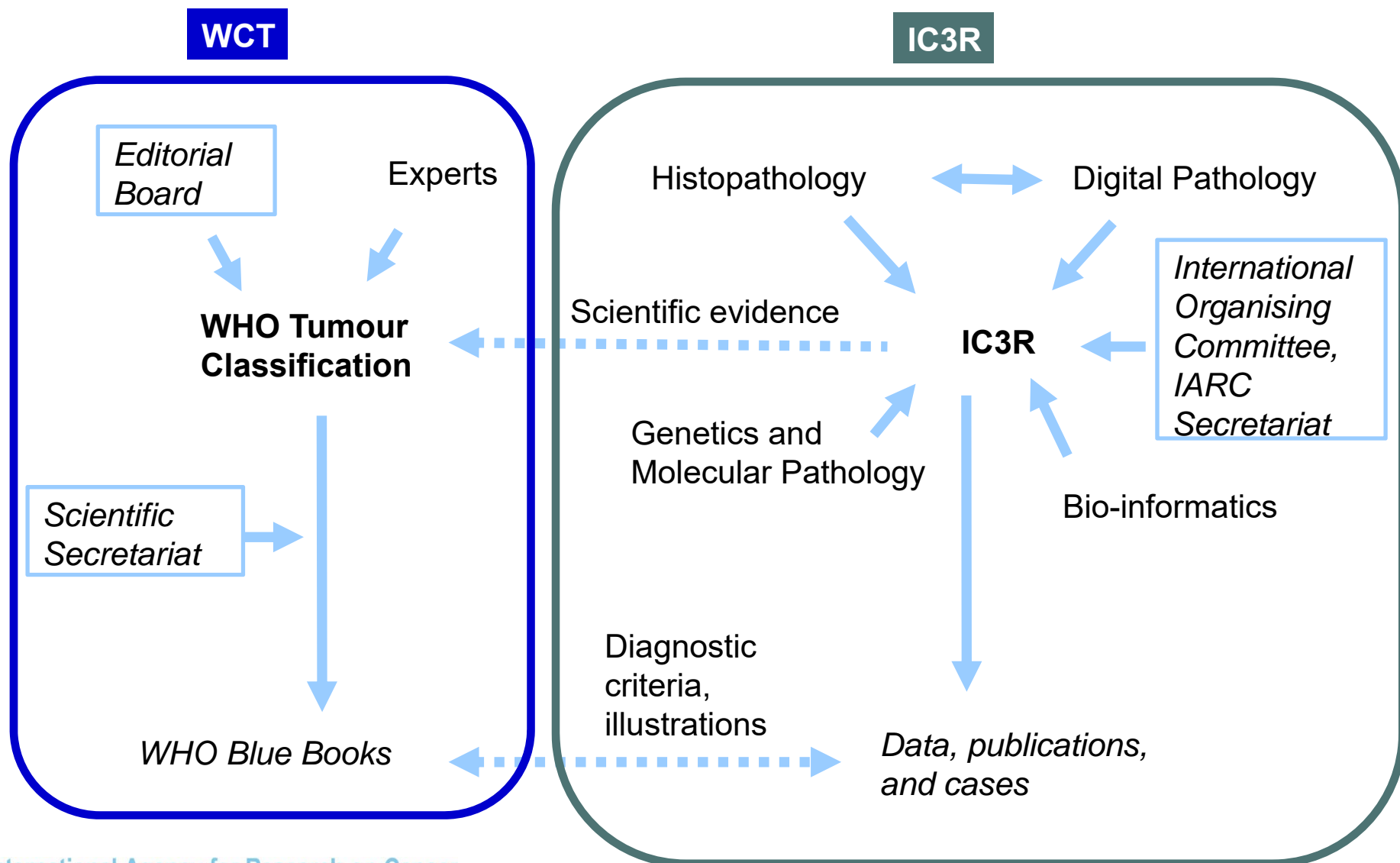
- Contopoulos-Ioannidis DG, et al. Life Cycle of Translational Research for Medical Interventions. *Science* 2008, 321:1298-1299.
- Douet et al., An exploratory investigation of the influence of publication on translational medicine research *Journal of Translational Medicine* 2010, 8:62

## *Current challenge: Information overload...*

Multiple organizations are involved in collating information across the different aspects of cancer classification, often in isolation from each other, including:

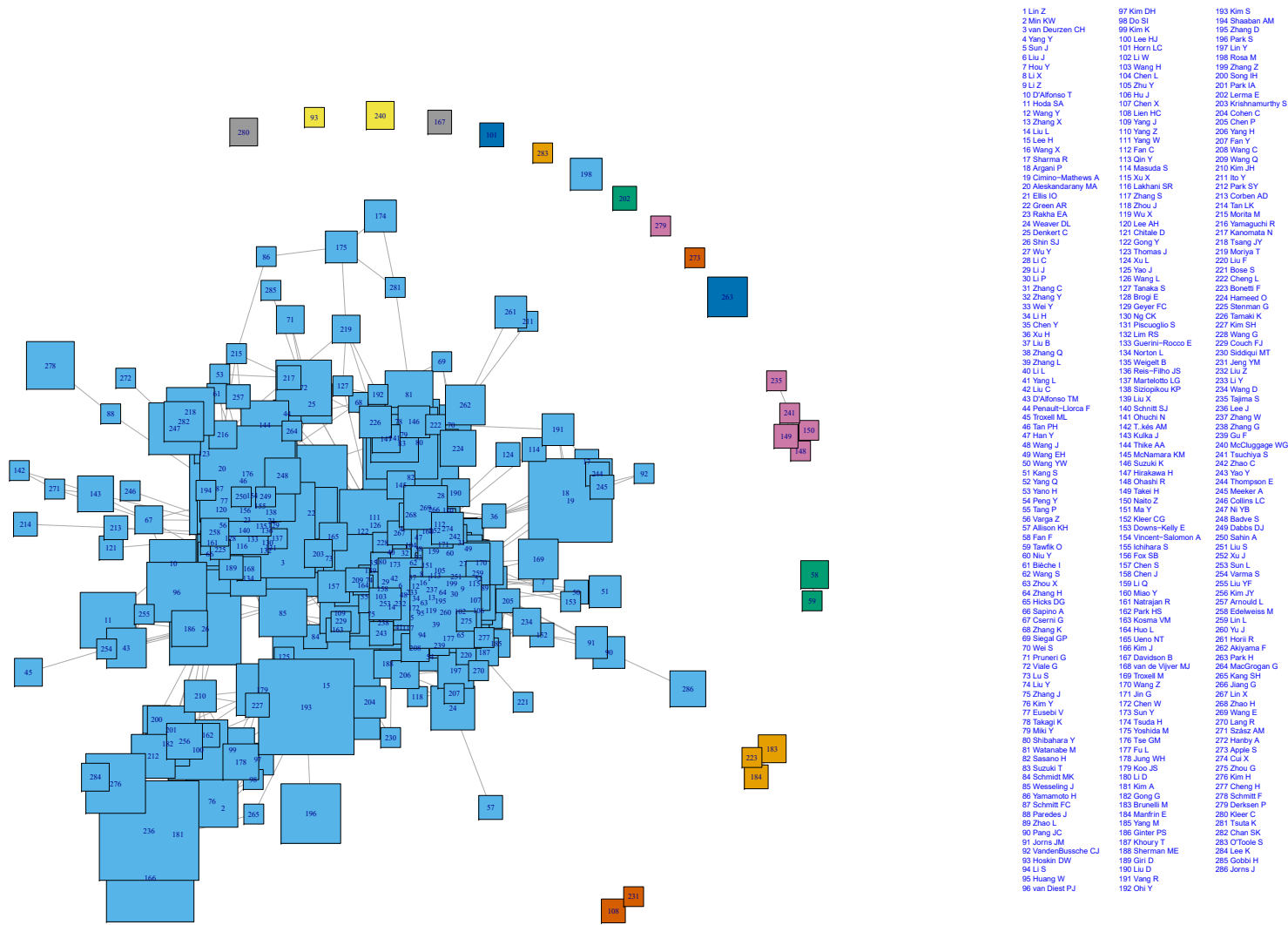
- International organizations in histopathology and genetics,
  - Professional bodies
  - Research institutes
  - Healthcare providers.
- 
- High-level collaboration to provide the high-quality information and evaluation required.
  - We are therefore proposing a high level Collaboration for Cancer Classification and Research (IC3R)

# Collaboration for Cancer Classification and Research (IC3R)



International Agency for Research on Cancer

# Bibliometrics for BB5...



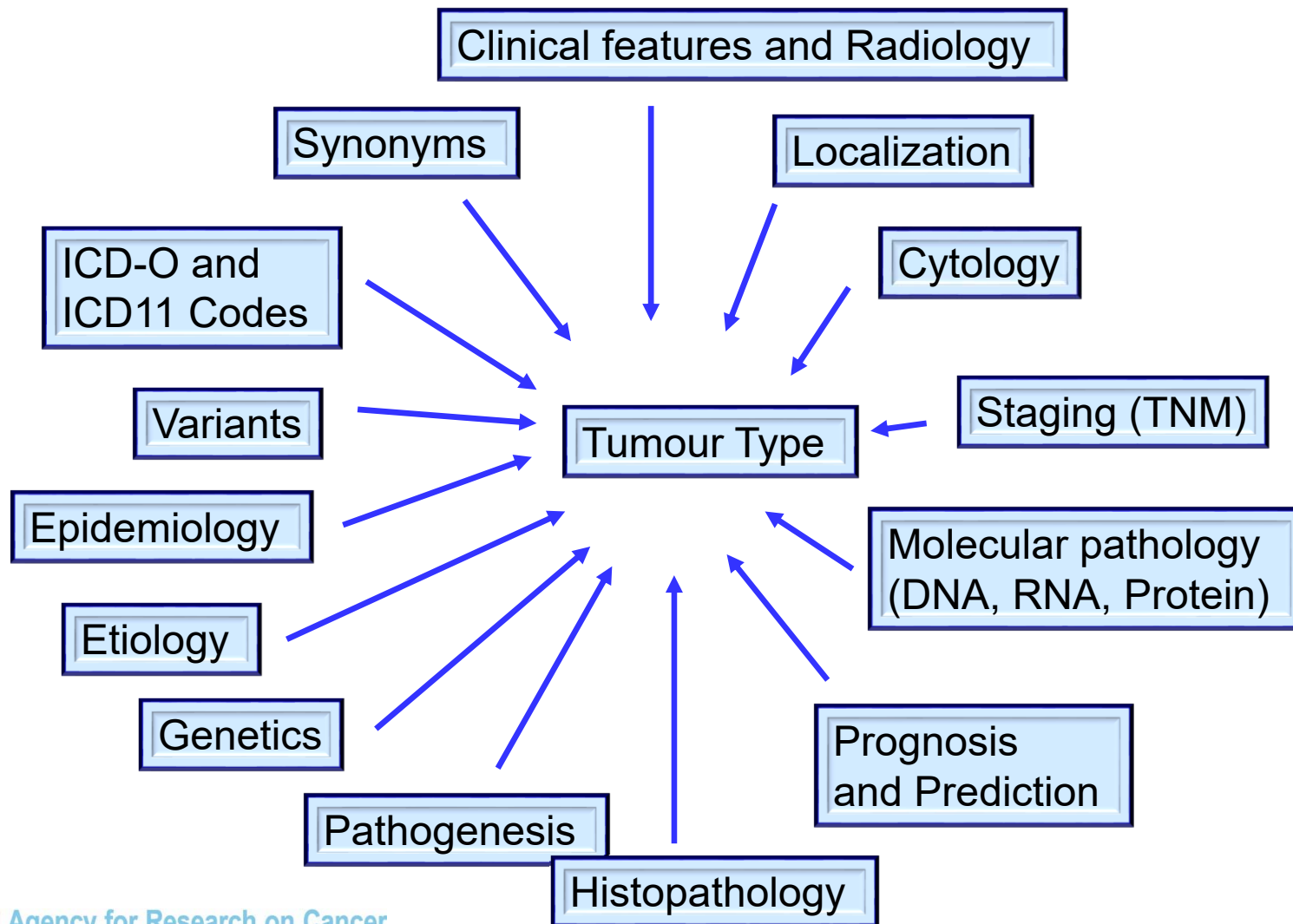
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# *Classification terms*

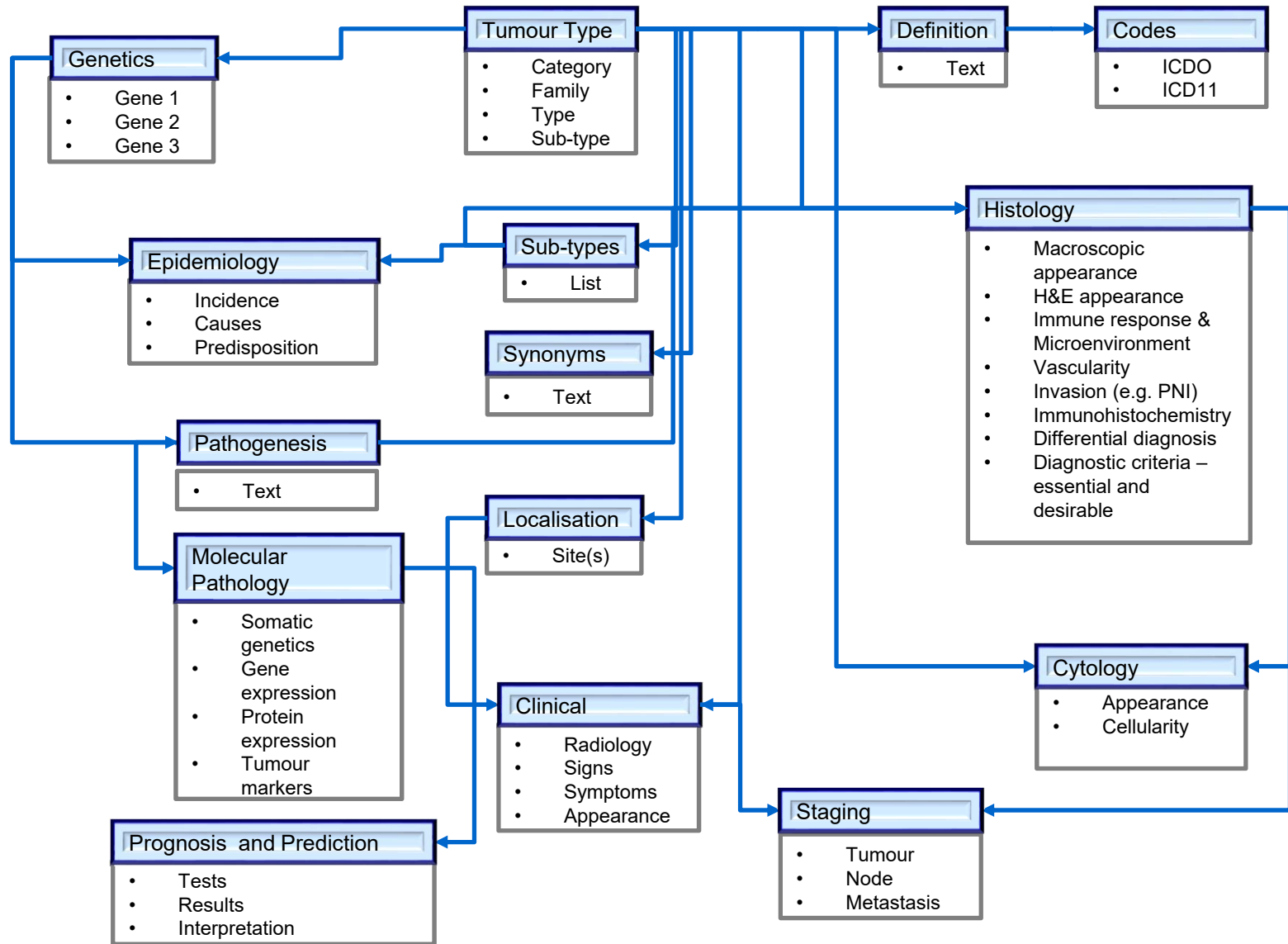
- *Site*, e.g. Stomach
- *Category*, e.g. Epithelial neoplasms
- *Family (Class)*, e.g. Adenomas and other premalignant neoplastic lesions
- *Type*, e.g. Adenoma
- *Variant (Sub-Type)*, e.g. Pyloric-gland type

Stage and Grade are dealt with separately....

# *The multi-dimensional nature of cancer classification*



## The multi-dimensional nature of cancer classification



# *WHO BB Layout (5th Series) DRAFT*

- Definition
- ICD-O and ICD11 Codes
- Related Terminology (Synonyms)
- Subtypes (Variants)
- 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)

# Neuroendocrine neoplasms

- The classification of neuroendocrine neoplasms (NENs) differs between organ systems and currently causes considerable confusion.
- A uniform classification framework for NENs at any anatomical location may reduce inconsistencies and contradictions among the various systems currently in use.
- *Site:* nearly anywhere
- *Category:* Neuroendocrine neoplasms
- *Families:* based on genetic and histological differences
  - Neuroendocrine tumour
  - Neuroendocrine carcinoma
- *Type:* Many, based on hormone secretion...
- *Grade:* based on proliferation

# Working classification

- We have provided a framework for a common classification of NENs.
- Morphology is the primary basis for this classification, supported in some sites by underlying genomic alterations.
- A basis for the next generation of NET classifications
- Consistent taxonomy to understand how neoplasms from different organ systems inter-relate genetically.
- Recognition of site-specific differences among NENs, of critical importance for proper diagnosis and clinical management.

Rindi G, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018 Aug 23. [PMID: 30140036]

## *The 5<sup>th</sup> Series WHO Classification of Tumours*

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

<http://whobluebooks.iarc.fr>





**WHO Classification of Tumours 5th Edition, 1st Editorial Board, Digestive System  
5-6 February 2018, IARC, Lyon, FRANCE**



International Agency for Research on Cancer



# WHO Blue Books Faculty



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# Changes in 5<sup>th</sup> Edition WHO Classification of Tumours: Digestive System Tumours

- Oesophagus: known sequence of progression of neoplasia, from inflammation to metaplasia (Barrett Oesophagus), dysplasia, and finally adenocarcinoma, driven initially by gastro-oesophageal reflux disease.
- Stomach: Most “epidemic gastric cancers” are now regarded as inflammation-driven cancers and the etiology is characteristically environmental, usually due to *Helicobacter pylori* infection. This infectious etiology results in the inclusion of gastric cancer among the restricted list of highly lethal, but preventable cancers.
- Rare tumours have distinctive driver mutations that have been identified – for instance ,the characteristic gene fusion MALAT1-GLI1 in gastroblastoma, and EWSR1 fusions in gastro-intestinal clear cell sarcoma and malignant gastro-intestinal neuroectodermal tumour.

# *Breast Tumours*

- Well, that would be telling!
- It will cover recent advances in molecular understanding of breast tumours, including prognostic factors and predictive biomarkers.
- Where there is level 1 or 2 evidence, you can expect changes.
- There will be a separate chapters on haematolymphoid neoplasms of the breast, soft tissue tumours, and inherited tumour syndromes
- The editorial board meets in December and I hope to have a book for you in summer 2019.

# Conclusion

- There is a need for all pathologists 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!*



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