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

International Agency for Research on Cancer
Lyon, France

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International Agency for Research on Cancer
World Health Organization

Declaration of Interests

- Pathologist at the International Agency for Research on Cancer, part of the World Health Organization.
- Honorary Professor of Pathology at University College London and Coventry University.
- Previously involved in molecular pathology designing and validating assays.
- Currently involved in computational pathology research.
- All opinions expressed are personal, and not those of any of the organisations listed.

5th Edition WHO Classification of Tumours

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5th 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^2 not HPF)
- Epidemiology – from IARC 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
Faculty

300,000 (estimate)

60,000 – mainly pathologists

1,800 (150 per book)

20 standing + 144 expert

WCT Blue Books team

The 5th Series WHO Classification of Tumours (updated May 2019)

- 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
- Haematolymphoid Tumours
- Head and Neck Tumours
- Endocrine Tumours
- Skin and Adnexa Tumours
- Eye and Orbit Tumours
- Neuroendocrine Tumours
- Hereditary Tumours

http://whobluebooks.iarc.fr

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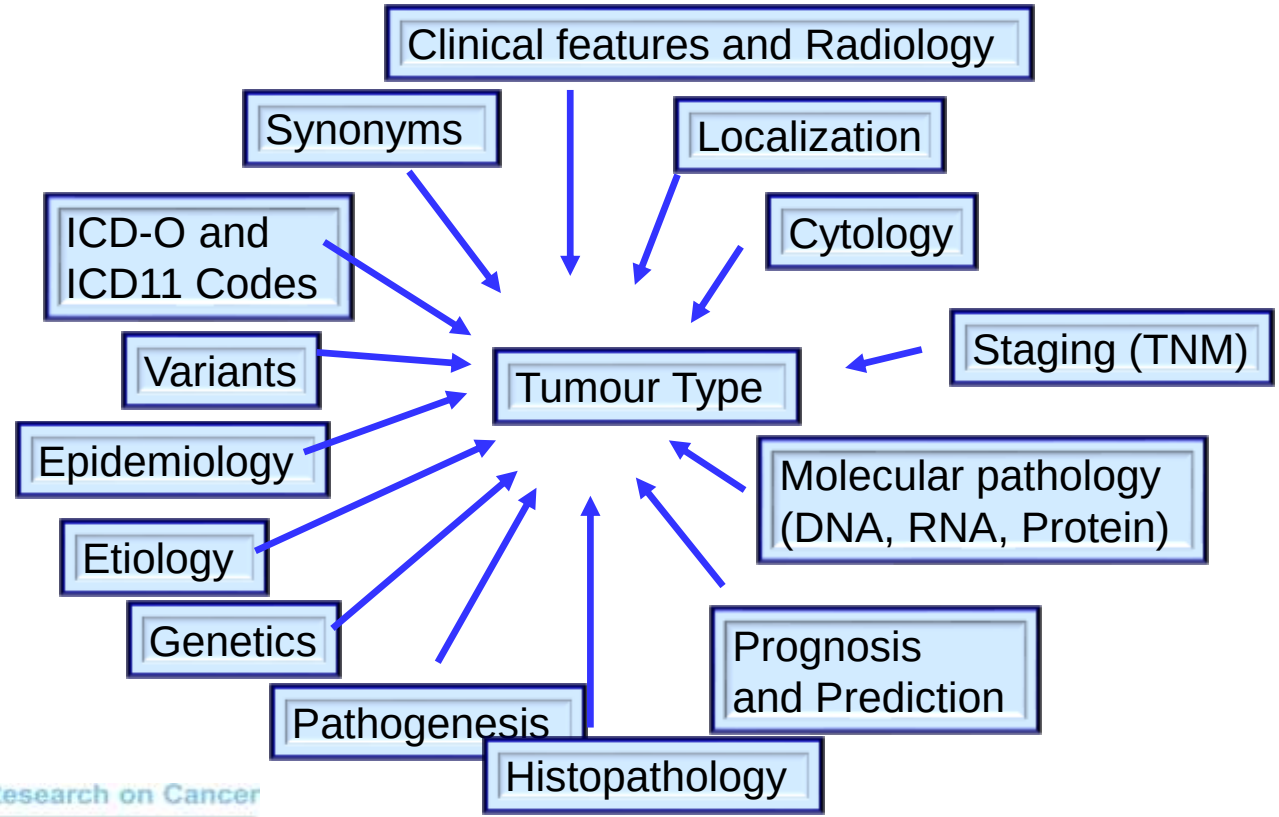
Classification terms

- *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 multi-dimensional nature of cancer classification



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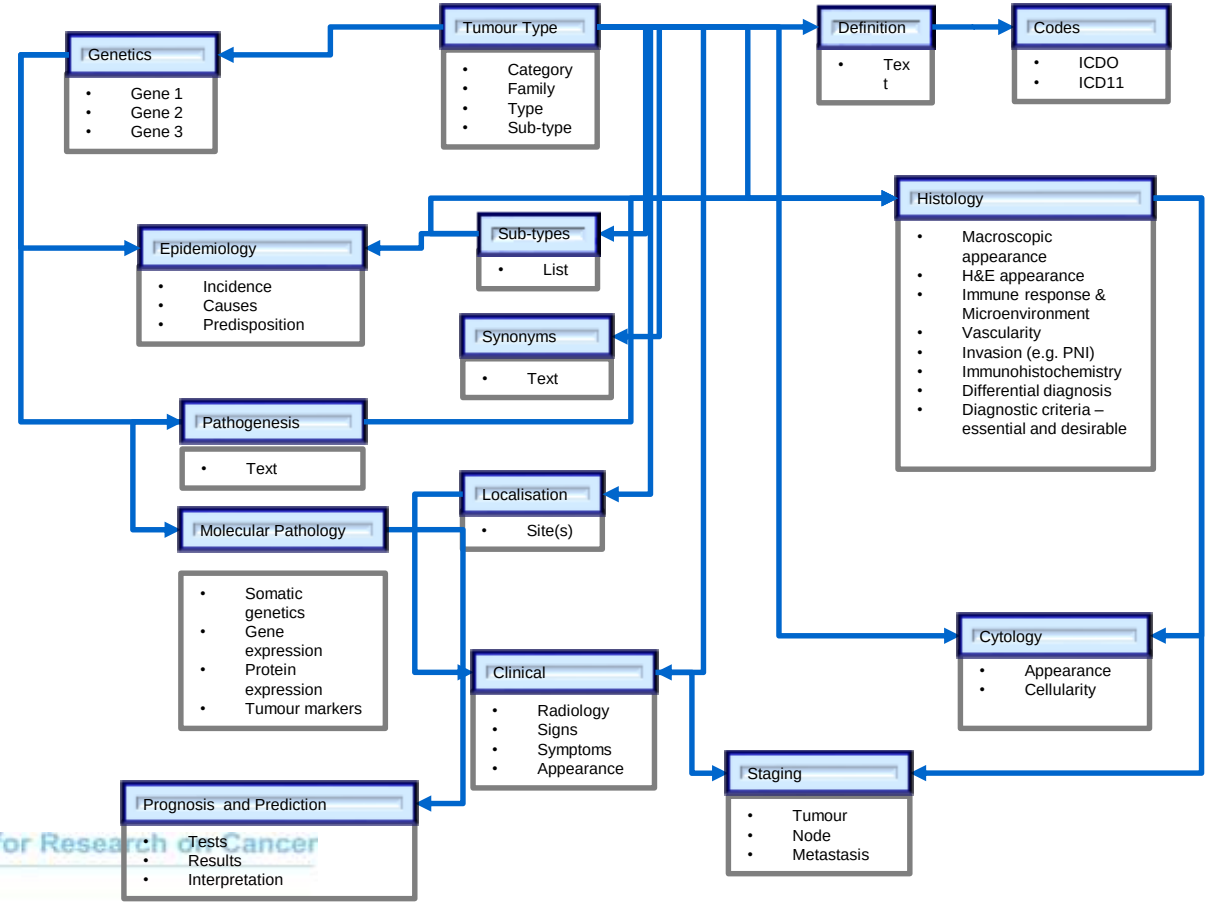


WHO BB Layout (5th Series) DRAFT

- 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)

Challenges for tumour classification

- Translation of evidence to practice
- Quality of evidence
- Quality of measurements e.g. mitosis
- Quality of genomic notation
- Naming tumor syndromes
- Information overload

Current challenge - Translation

- 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: Quality of evidence

- 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

- 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'

BRAF	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.

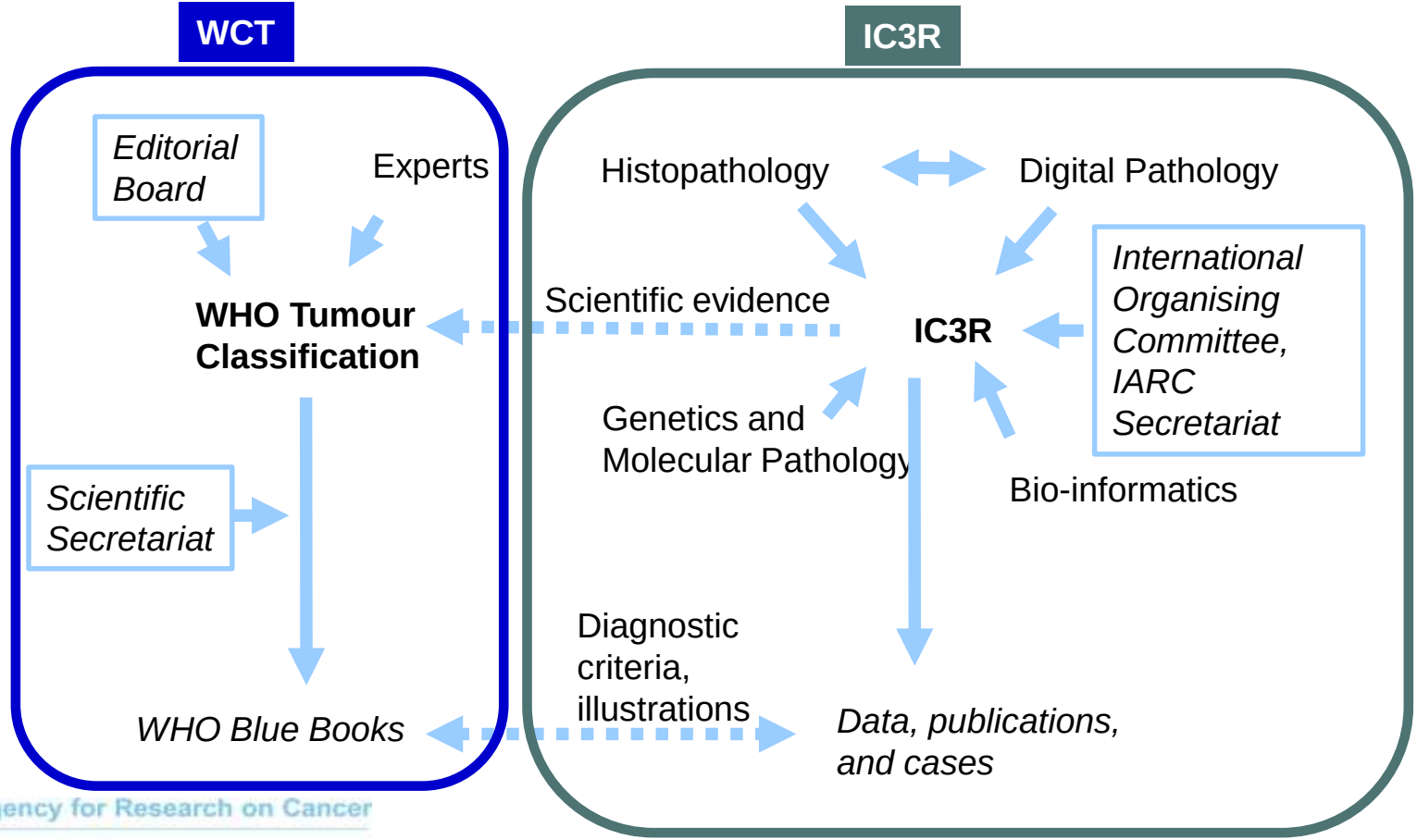
Current challenge: Information overload…

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 therefore proposed a high level Collaboration for Cancer Classification and Research (IC3R), and the first meeting was held in February.

IARC Collaboration for Cancer Classification and Research (IC3R)



IARC Collaboration for Cancer Classification and Research (IC3R)
Inaugural Meeting, 4-5 February 2019, Lyon

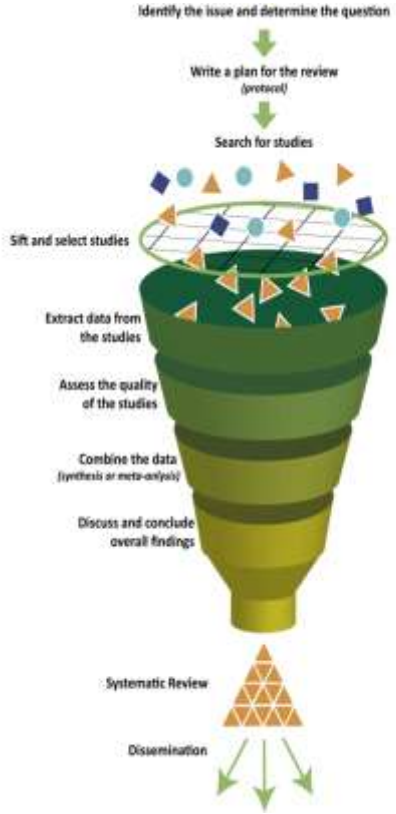
Aims

Our vision is to create a collaboration framework termed the "IARC Collaboration for Cancer Classification and Research (IC3R)".

Aims:

- IC^{3}R will be tasked with:
  - Harmonizing cancer-related data generated by IC3R members,
  - Standard-setting for analytical procedures,
  - Identification of critical gaps (e.g. non-uniform annotations, classifications, bioinformatics)
- IC^{3}R will act in close collaboration with others in the field.
- IARC will not physically host the large data sets: it will provide the secretariat,
- We hope that the formation of such a forum will allow the generation of standards and procedures which will benefit all parties involved.

Systematic review process and tools



Review question format and structure

Reference management software

Data extraction form

Appropriate method for data synthesis

Database and search tools

Results reporting: PRISMA flow diagram

GRADE Summary of Findings table

Forest plot

Source: Adapted from Cochrane Infographics: The Concept of a Systematic Review. Available at https://cccrg.cochrane.org/infographics

Conclusion

- Information overload is a real problem for cancer classification and therefore for tumour diagnosis.
- IC3R will harmonise data collection, encourage standards for data collection and seek to improve data quality.
- 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!