From Implementing Digital Pathology to IC^{3}R

International Agency for Research on Cancer
Lyon, France

Ian A Cree FRCPath
Head, WHO Classification of Tumours

creei@iarc.fr

Declaration of Interests

- International Agency for Research on Cancer
- World Health Organisation
- Previously at U.K. NHS overseeing implementation of GE Omnyx digital pathology in Coventry

- 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

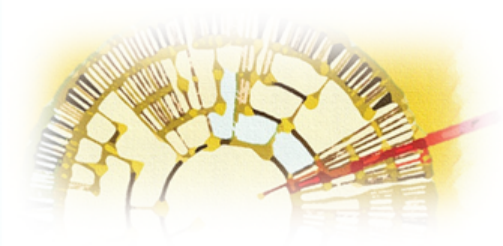
IARC and WHO

A complementary partnership

Research IARC on cancer prevention

World Health Organization

Evidence-base



for cancer prevention and control programmes

International Agency for Research on Cancer

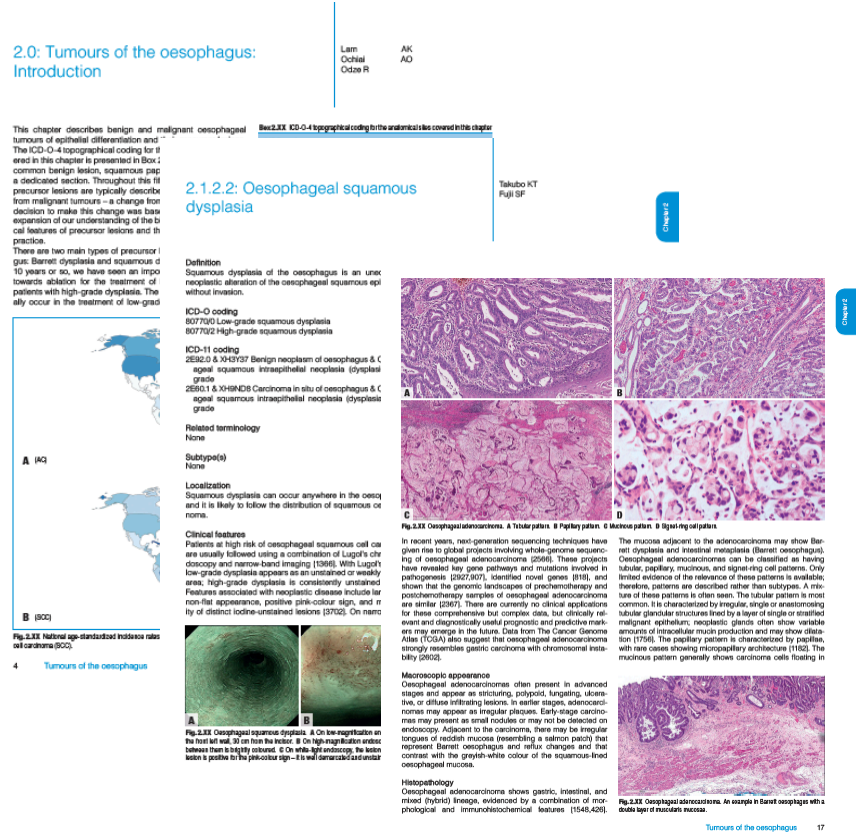
World Health Organization

Translates the scientific evidence

into guidelines and policies

IARC – an influential publications programme

WHO Classification of Tumours

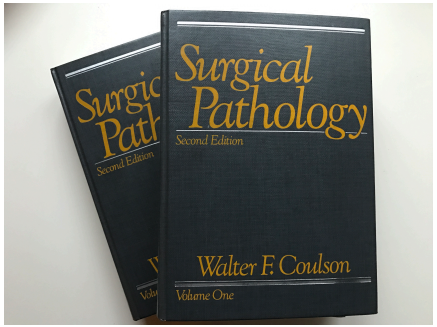


International Agency for Research on Cancer

World Health Organization

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

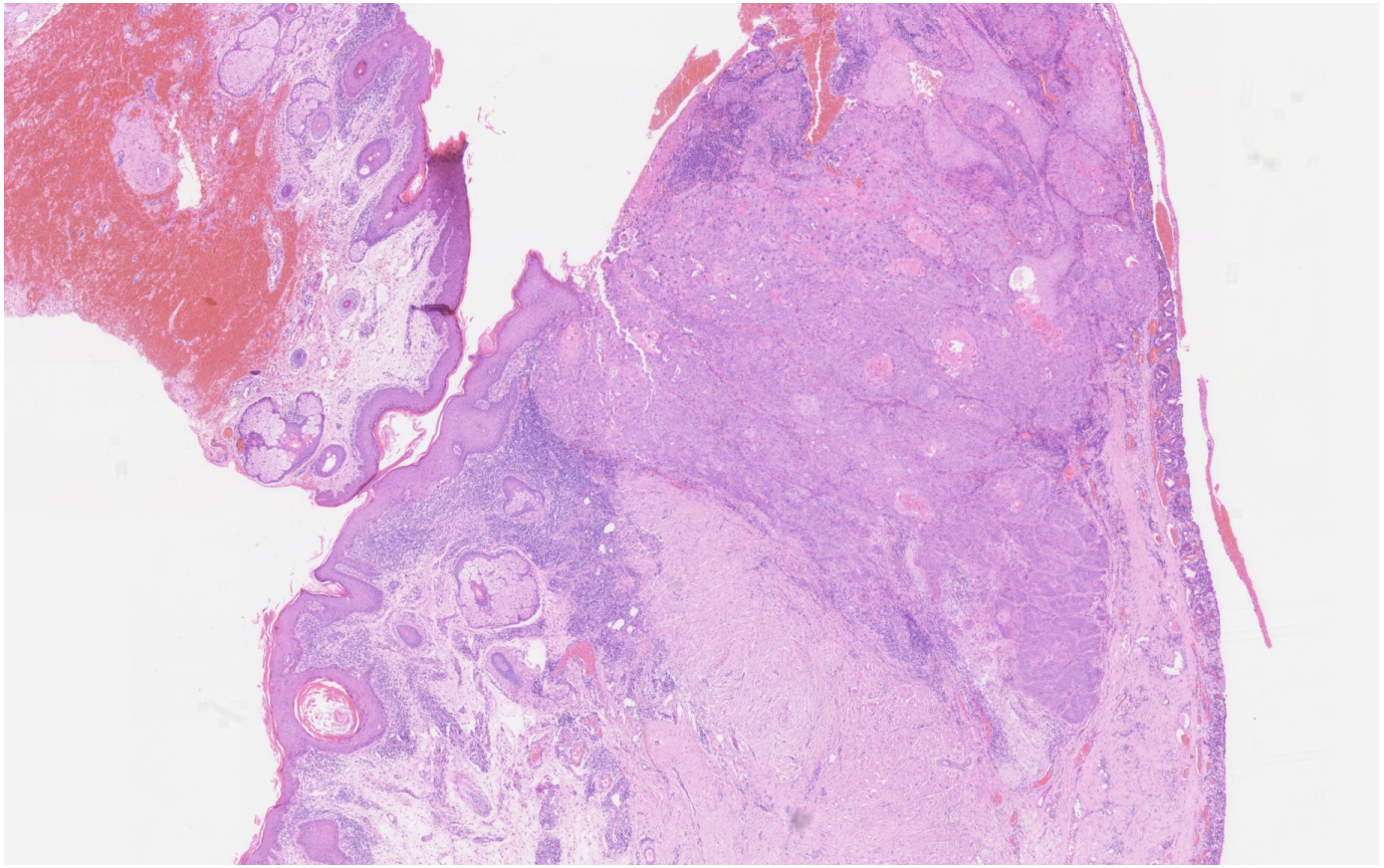
- Microscope
- Dusty bookshelves full of out of date texts (I bought the last one, and the diagnoses haven't changed much…)
- Internet if you're stuck?
- Immunohistochemistry works well...does anyone use electron microscopy anymore?
- Better send off a few sections for molecular pathology – I wonder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

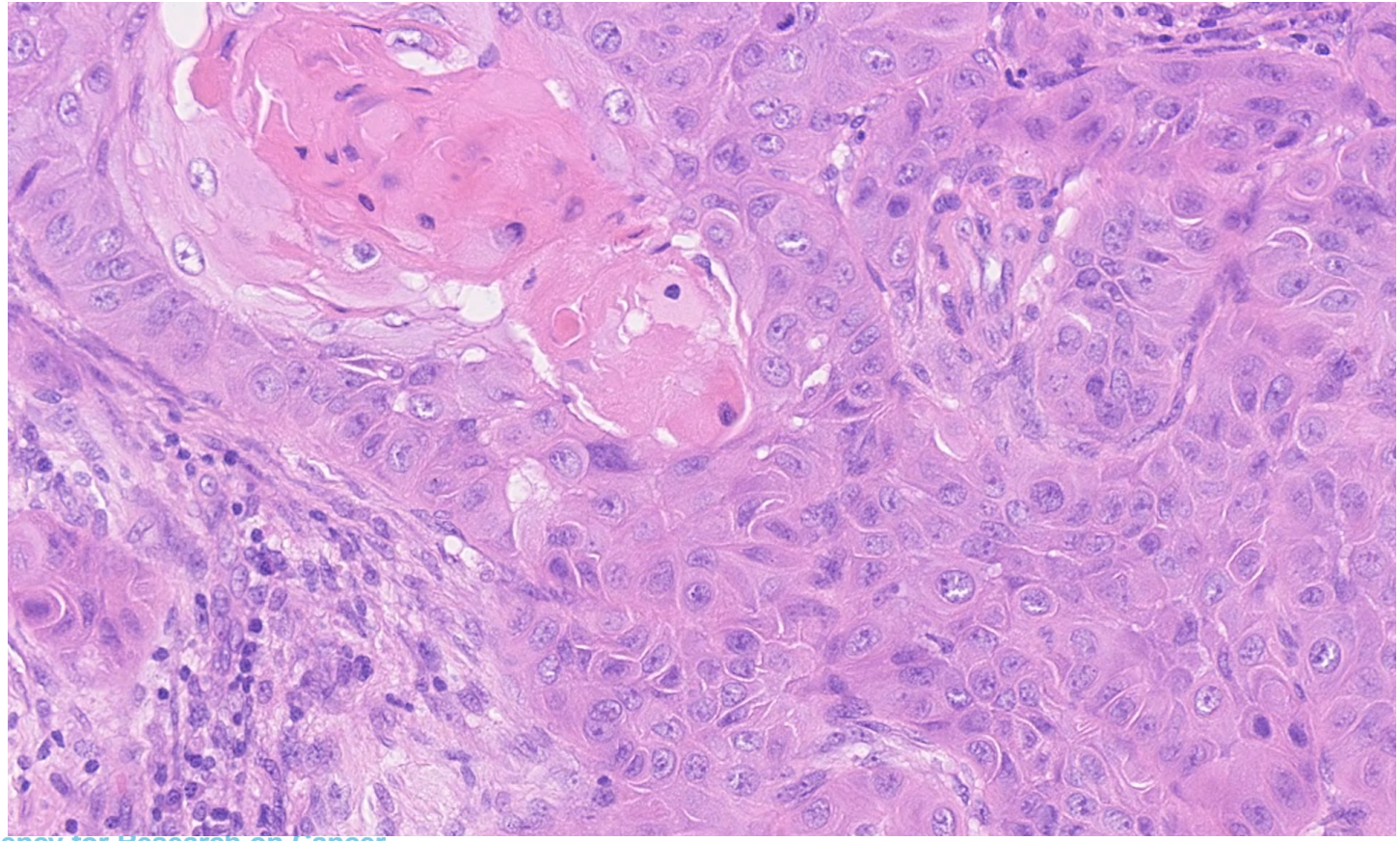
Pathology of the Future?

- Digital pathology with computer assisted 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?
- Predictive measurements to underpin treatment.
- Continuous education…books?

Digital Pathology: Intuitive, Easy To Use, Automatic


No Case Selected
Leica





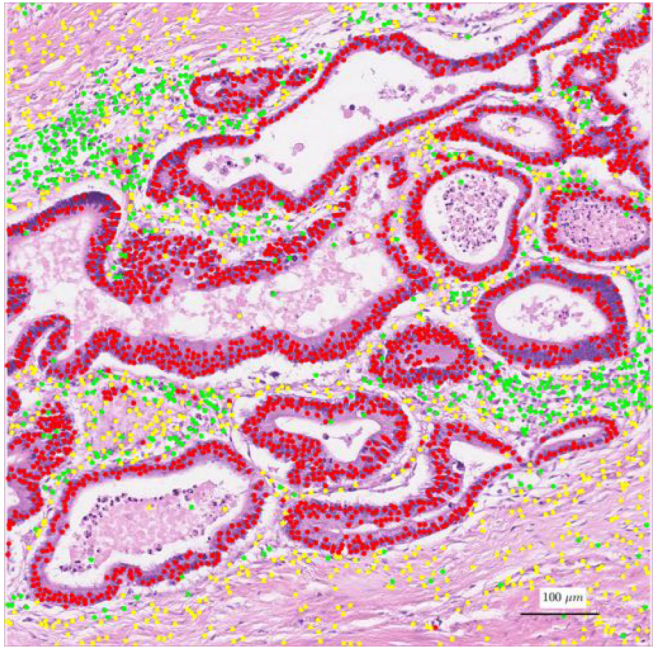
Validation study

- 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.

Tools becoming available

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



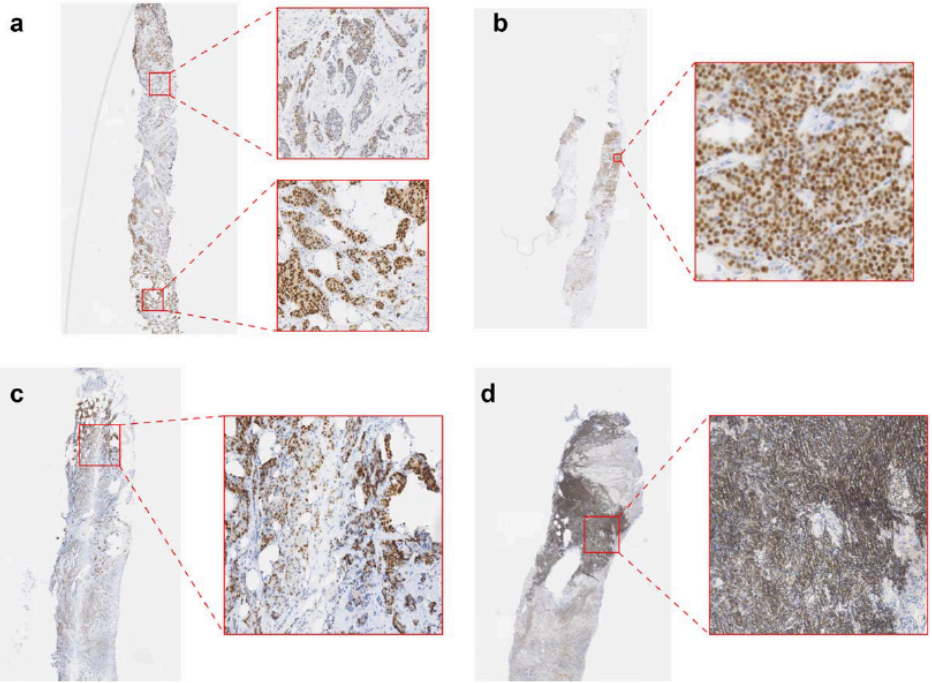
Siriniukunwattana K, et al. IEEE Transactions 2016.

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.



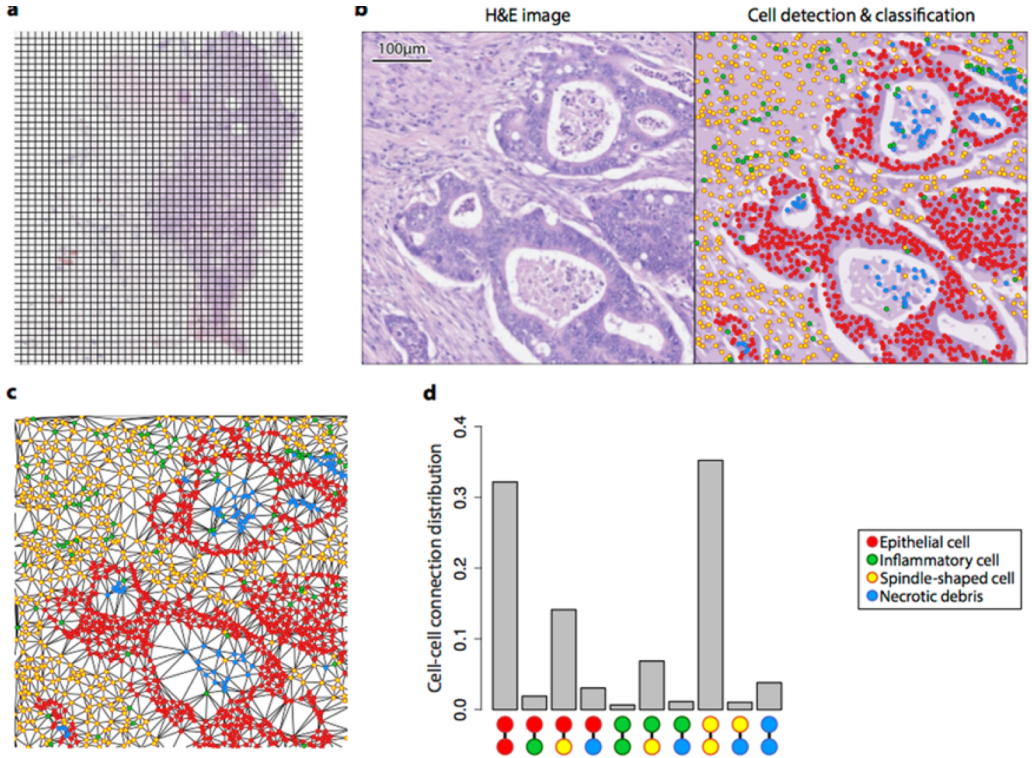
Out of focus WSI

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.

Why go digital?

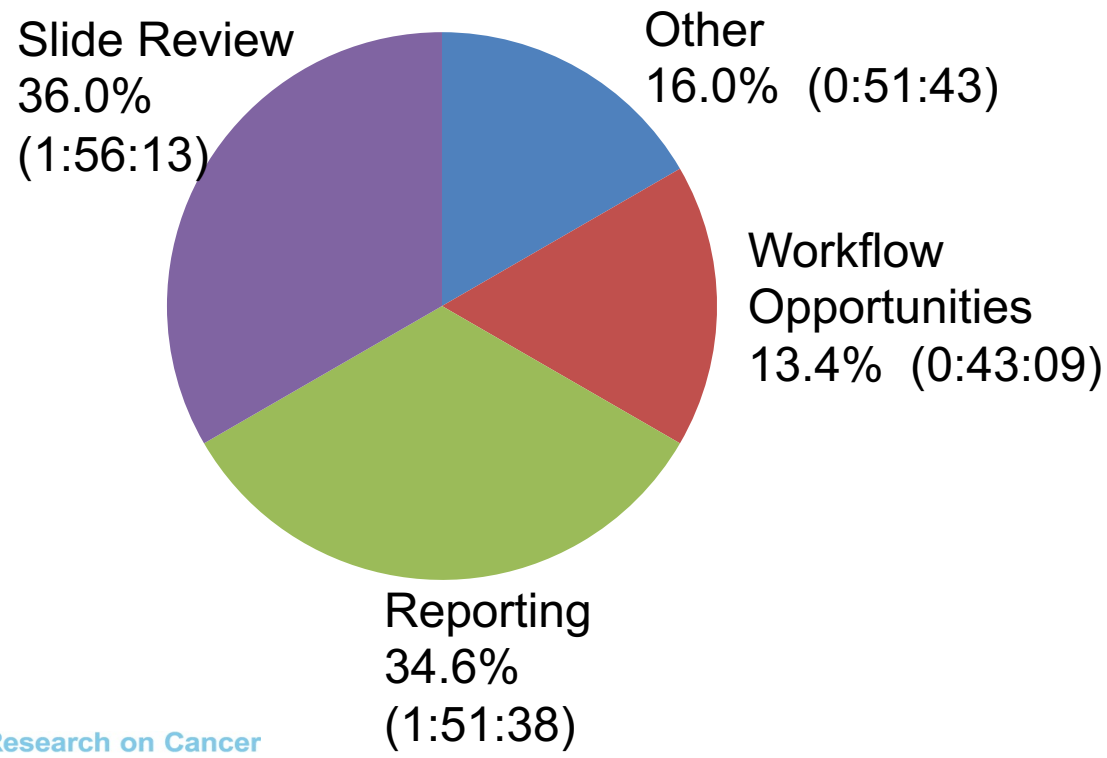
- Economic reasons
    - Increase efficiency of pathologists
    - Reduce turn around time to report cases
    - Improved review of cases including MDT review
- Quality advantages
    - Reduced error rate
    - Increased sub-specialisation
    - IHC scoring and indexing
    - Tumour grading / dysplasia grading
    - Cancer finder – AI methodology in practice

Economic argument

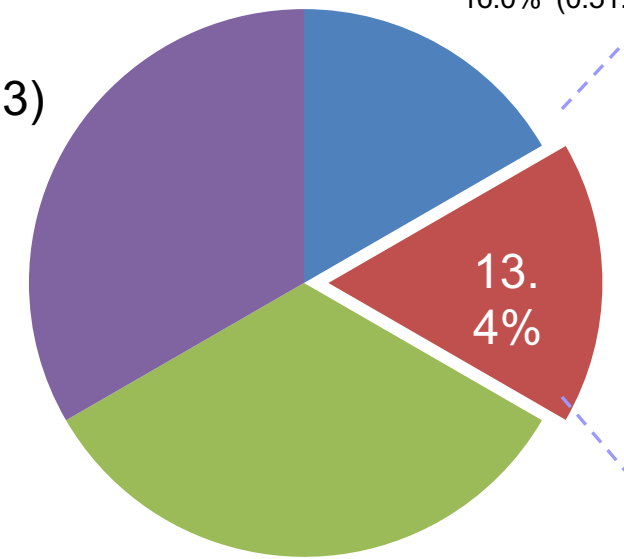
- 12-13% (claimed) efficiency gain at pathologist level
- Saving on retrieval of archived slides

- Merger of departments saving pathologist numbers
- Reduced turn around time changes patient pathways
    - reducing visits and in-patient time
    - better more efficient use of resources
- Facilitates review improving diagnostic accuracy

Pathologist T&M Study Results
Breakdown of Time Working Cases



Pathologist T&M Study Results
Breakdown of Workflow Opportunities



Workflow Opportunities

Organizing Cases (0:10:25)	24.1%
Querying for Cases (0:07:59)	18.5%
Waiting for Delivery (0:04:49)	11.2%
Matching (0:04:32)	10.5%
Searching for Cases (0:04:04)	9.4%
Transporting Cases (0:03:58)	9.2%
Other (0:07:21)	17.0%

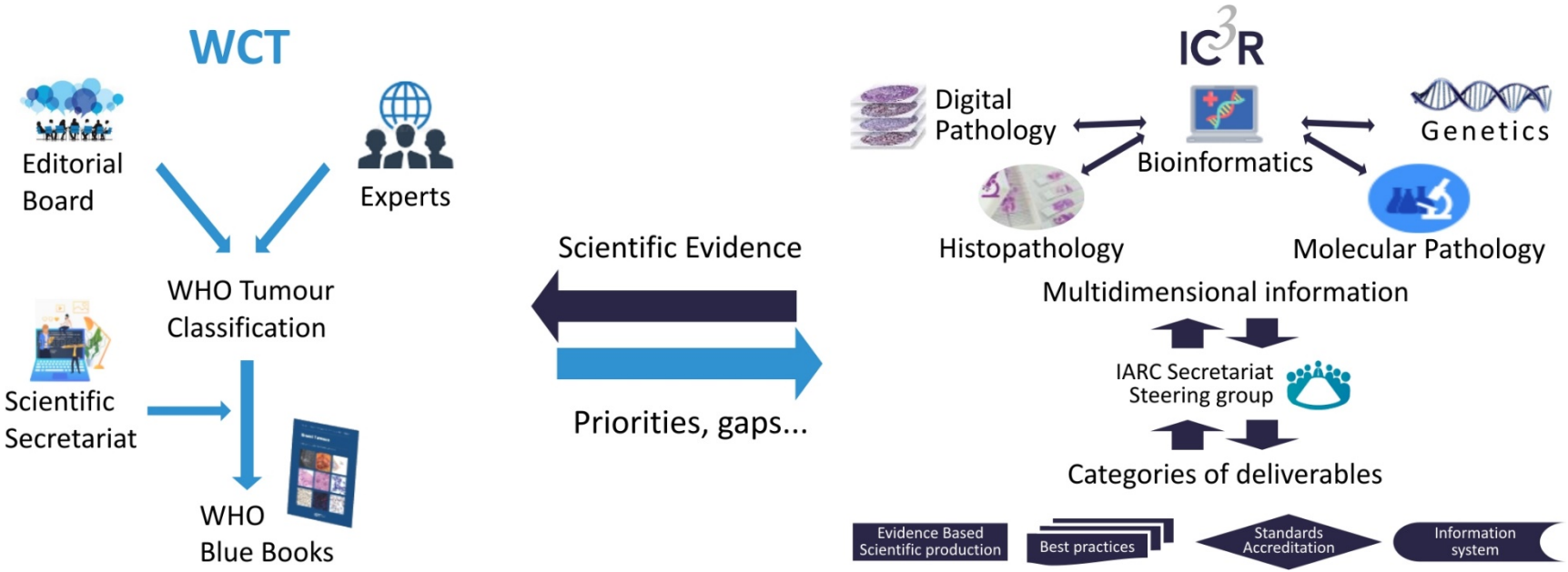
100% (0:43:09)

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

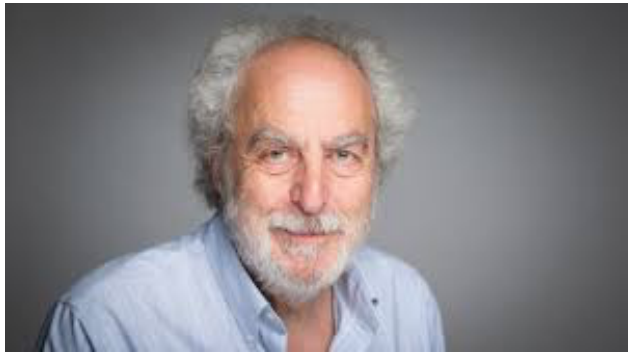
IC^{3}R will provide a forum for encouraging high quality research, and for coordinating evidence generation, synthesis, and evaluation, for tumour classification. Member institutions include universities, research centres and other interested parties, that will assign representatives to discuss and 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

IC³R Framework



Dichotomising continuous variables



Doug Altman, 1948 - 2018

equator network

http://www.equator-network.org

STATISTICS IN MEDICINE
Statist. Med. 2006; **25**:127–141
Published online 11 October 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.2331

Dichotomizing continuous predictors in multiple regression: a bad idea

Patrick Royston[1,*,†], Douglas G. Altman[2] and Willi Sauerbrei[3]

[1]*MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, U.K.*
[2]*Centre for Statistics in Medicine, University of Oxford, Wolfson College Annexe, Linton Road, Oxford OX2 6UD, U.K.*
[3]*Institute of Medical Biometry and Medical Informatics, University Hospital of Freiburg, Stefan-Meier-Str. 25, 79104 Freiburg, Germany*

Practice

Statistics Notes

The cost of dichotomising continuous variables

Douglas G Altman, Patrick Royston

Cancer Research UK/NHS Centre for Statistics in Medicine, Wolfson College, Oxford OX2 6UD
Douglas G Altman *professor of statistics in medicine*
MRC Clinical Trials Unit, London NW1 2DA
Patrick Royston *professor of statistics*
Correspondence to: Professor Altman doug.altman@cancer.org.uk

BMJ 2006;332:1080

Measurements of continuous variables are made in all branches of medicine, aiding in the diagnosis and treatment of patients. In clinical practice it is helpful to label individuals as having or not having an attribute, such as being "hypertensive" or "obese" or having "high cholesterol," depending on the value of a continuous variable.

Categorisation of continuous variables is also common in clinical research, but here such simplicity is gained at some cost. Though grouping may help data presentation, notably in tables, categorisation is unnecessary for statistical analysis and it has some serious drawbacks. Here we consider the impact of converting continuous data to two groups (dichotomising), as this is the most common approach in clinical research.[1]

What are the perceived advantages of forcing all individuals into two groups? A common argument is that it greatly simplifies the statistical analysis and leads preferable to performing several analyses and choosing that which gives the most convincing result. Use of this so called "optimal" cutpoint (usually that giving the minimum P value) runs a high risk of a spuriously significant result; the difference in the outcome variable between the groups will be overestimated, perhaps considerably; and the confidence interval will be too narrow. This strategy should never be used.[2,3]

When regression is being used to adjust for the effect of a confounding variable, dichotomisation will run the risk that a substantial part of the confounding remains.[4,5] Dichotomisation is not much used in epidemiological studies, where the use of several categories is preferred. Using multiple categories (to create an "ordinal" variable) is generally preferable to dichotomising. With four or five groups the loss of information can be quite small, but there are complexities in analysis.

Instead of categorising continuous variables, we pre-

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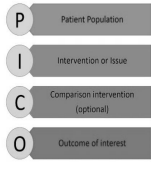
Systematic review process and tools

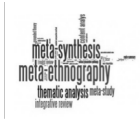
Review question format and structure

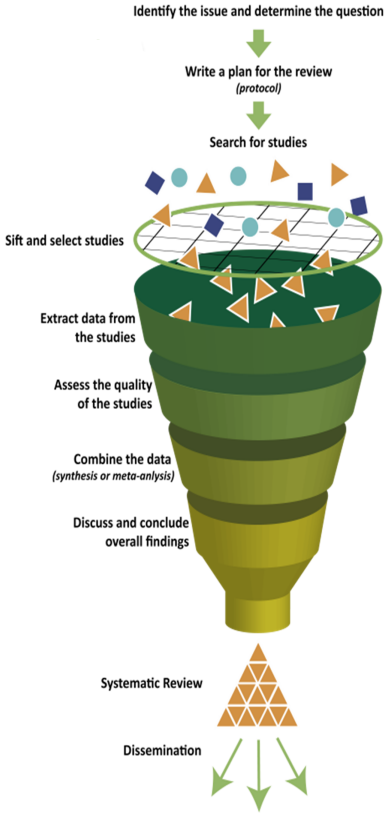


Reference management software

Data extraction form

Appropriate method for data synthesis



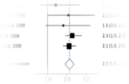


PubMed

Grey Literature Resources

SR TOOL BOX

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

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.

Thank you!

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