Using Human Tissue in Translational Research and Clinical Trials

Dr Bridget S Wilkins

NCRI Clinical Lead for Pathology Engagement

(Consultant Histopathologist, St Thomas' Hospital, London)

NCRI
National Cancer Research Institute

ECMC
Cellular and Molecular Pathology Network Group

What are the Pathology Samples?

- Blood and other biofluids obtained specifically for research.
- Tissue biopsy samples obtained specifically for research.
- Archived diagnostic tissue specimens that may be available for central review and/or (increasingly) for translational research.

Where are the Pathology Samples?

- In hospital pathology departments, in diagnostic archives.
- With reseachers, if sent directly.
- In biobanks (public or private):
  - Specific collections for research
  - Controlled conditions of collection, processing and storage
  - Detailed annotation

Where are the Pathology Samples?

- (In the patient – ‘walking donors’).

What's in the Diagnostic Archive?

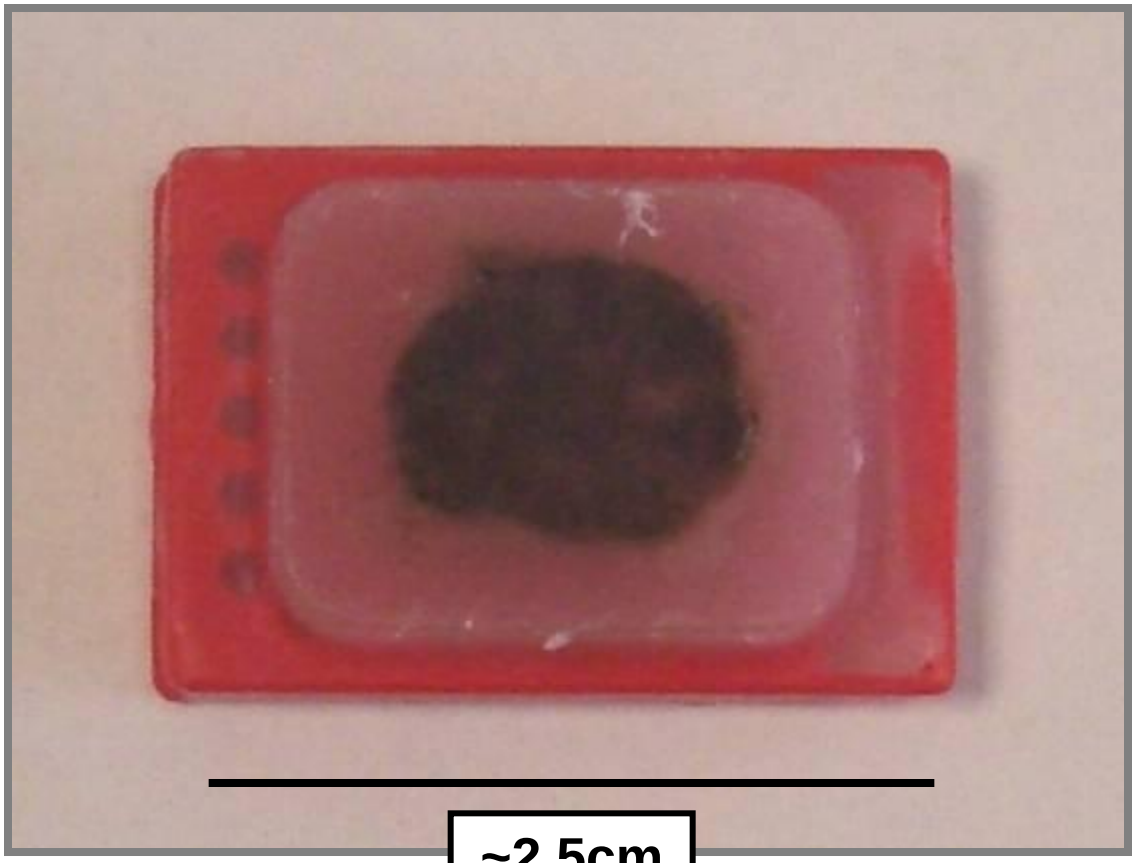
- Pathology departments in >200 NHS Trust hospitals each accumulate blocks of fixed, wax-embedded tissue from 10,000-60,000+ histology specimens per year.
- Only a small proportion of tissue samples are used up completely in patients' diagnostic tests.
- Blood and other biofluids are not usually kept but derived materials such as DNA may be.

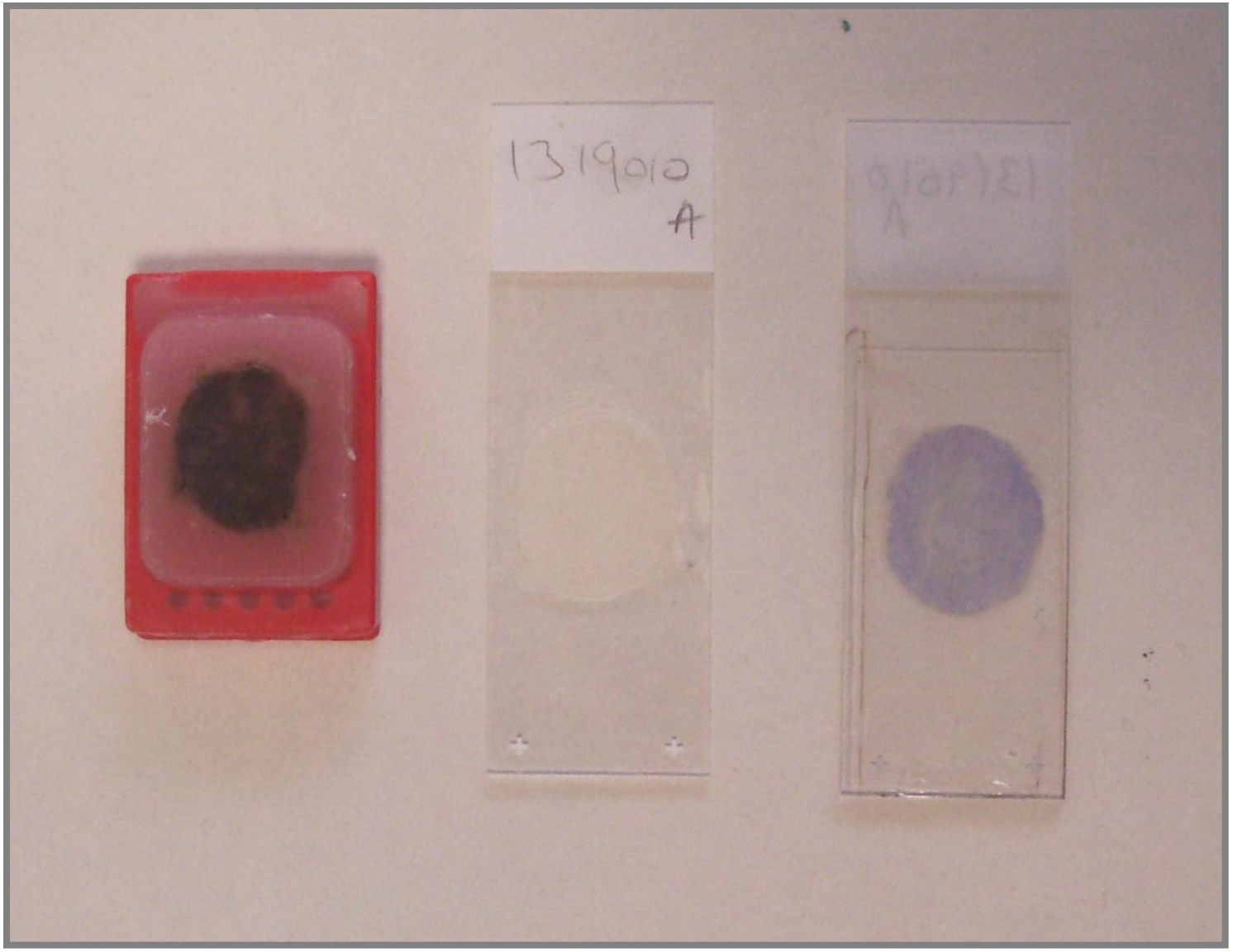
Why is Tissue Kept?

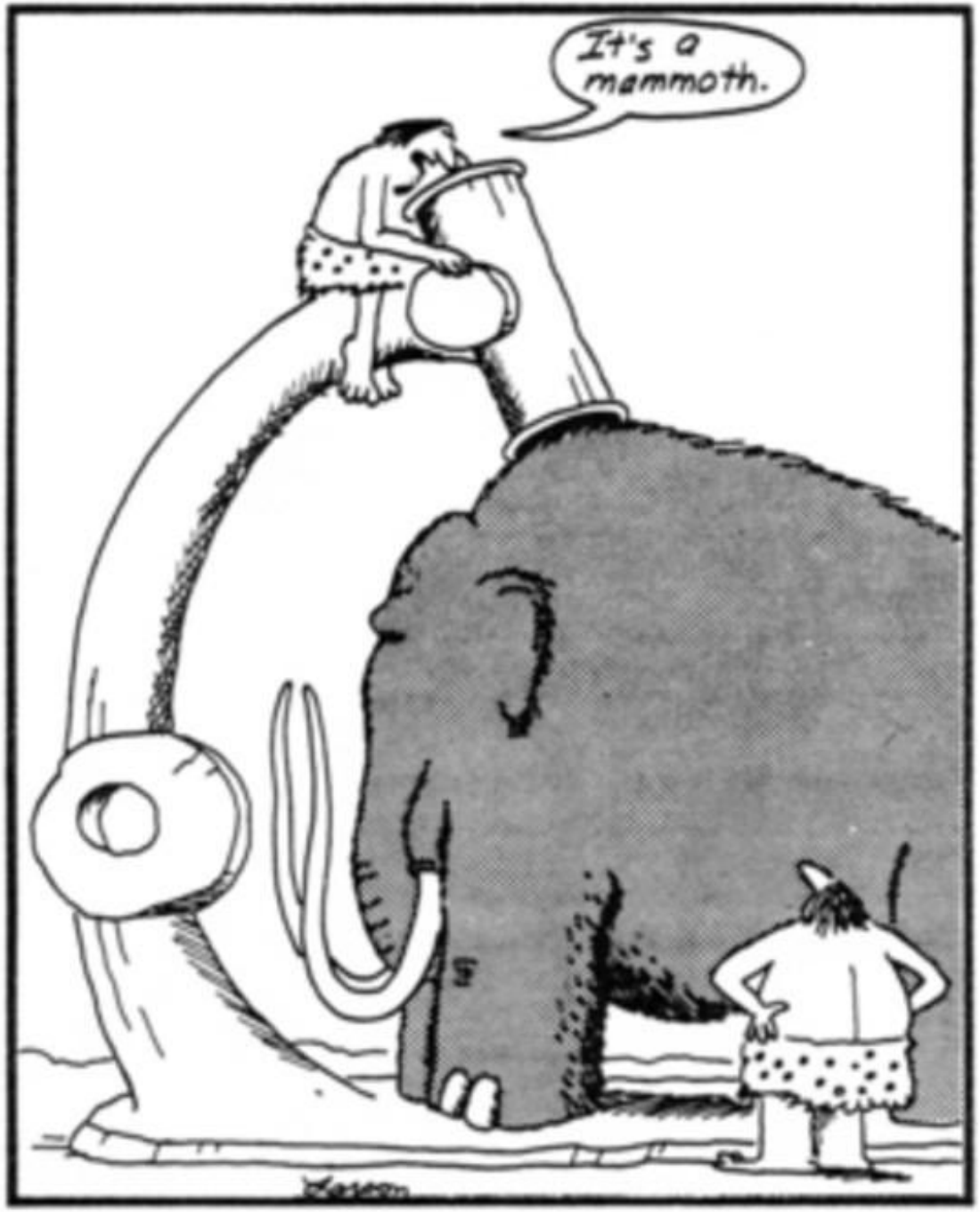
- Not primarily for research!
- Tissue blocks form a part of the patient's medical record.
- By law, any part of the medical record that cannot be replaced must be kept for 30 years.
- This is to allow review of the original findings, if required.
- It also means that new tests can be added retrospectively.

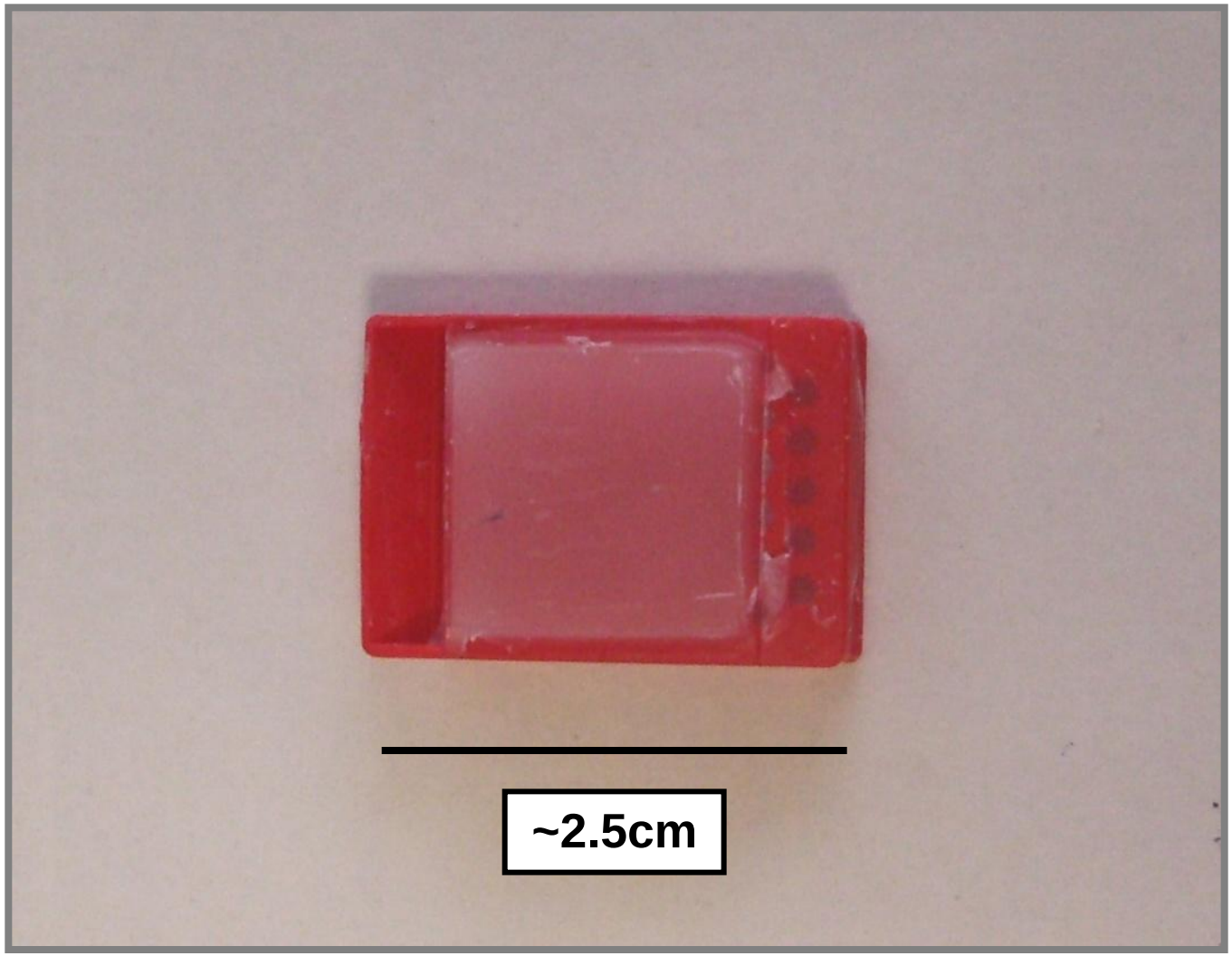
Why is Tissue Kept?

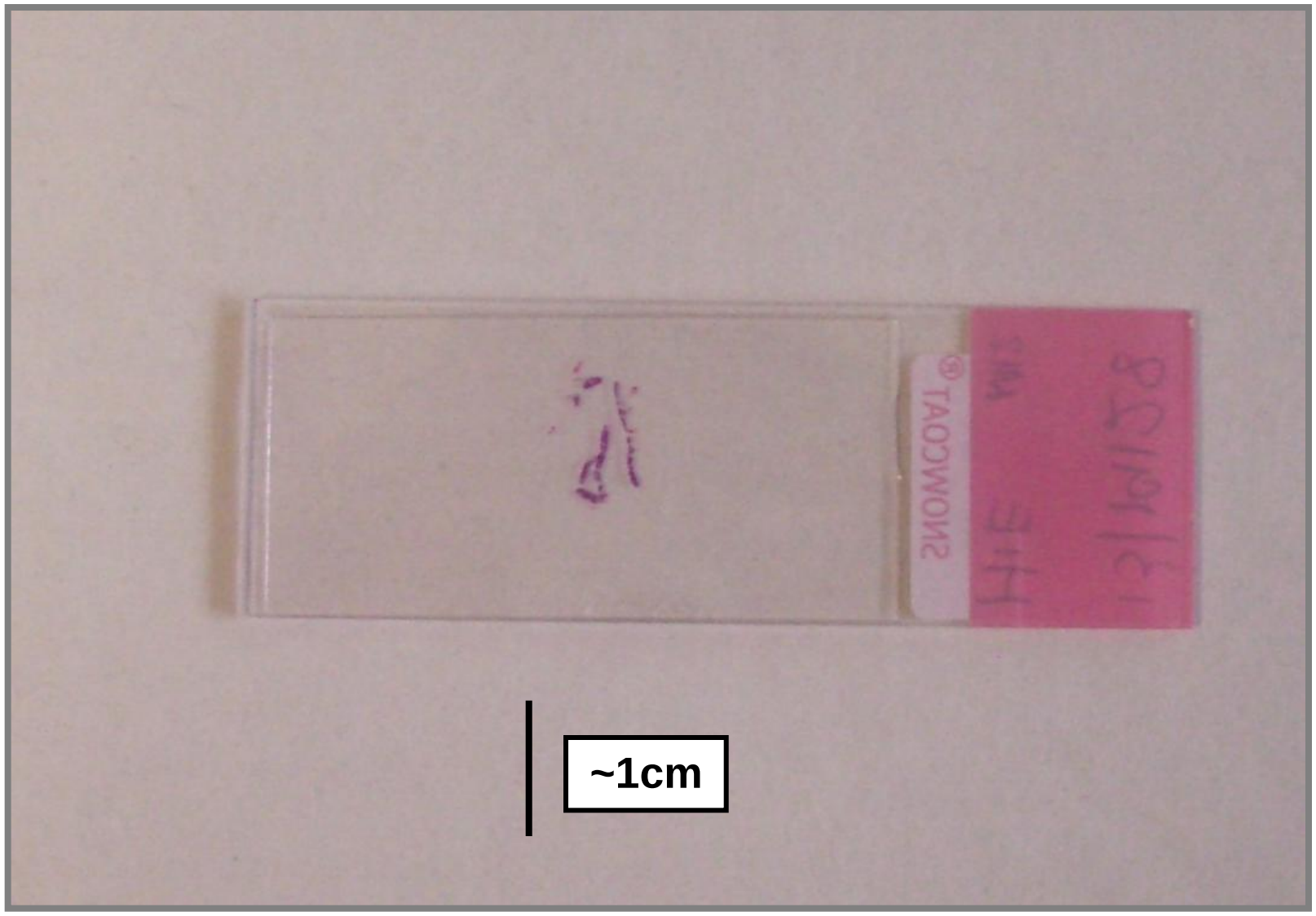
- The archive also contains huge numbers of glass slides, stained for microscopy.
- Overall, there are about 10 times as many of these as blocks.
- They can lawfully be discarded sooner, but rarely are - some are irreplaceable and sorting them out from the others is too complicated!


~2.5cm

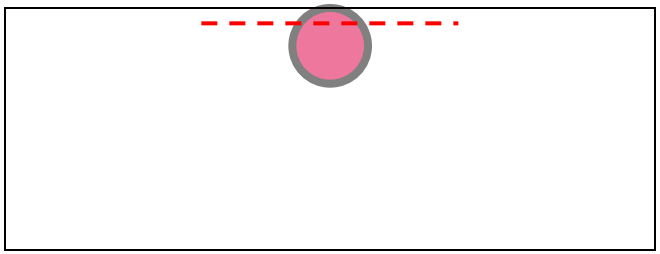

1319010
A


It's a mammoth.


~2.5cm


~1cm

How Much Tissue is in a Block?



Needle core 1mm diameter

= 1000 microns (μm)

Sections 2-3 microns thick

= 300-500 sections

Tissue slice 3-4 mm thick

= 3-4000 microns (μm)

Sections 2-3 microns thick

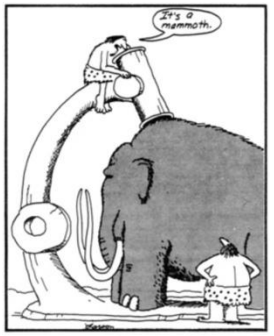
= 1000-2000 sections

Re-cutting uses ~20 sections each time for realignment and 'trimming in'

Is it Really ‘Surplus’ after Diagnosis?

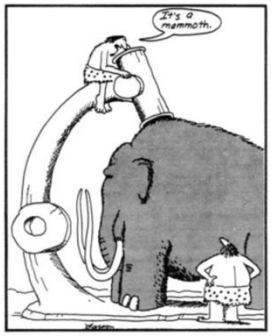
- Traditionally regarded so, but things are changing…
- Particularly in cancer medicine, we need more often to return to stored blocks to test them, sometimes after many years, to look for markers that a patient may respond to a new drug.
- We may also need to compare ‘old with new’ in future, to predict whether a patient’s cancer has changed over time and so may need different treatment.

Is it Actually Any Good?

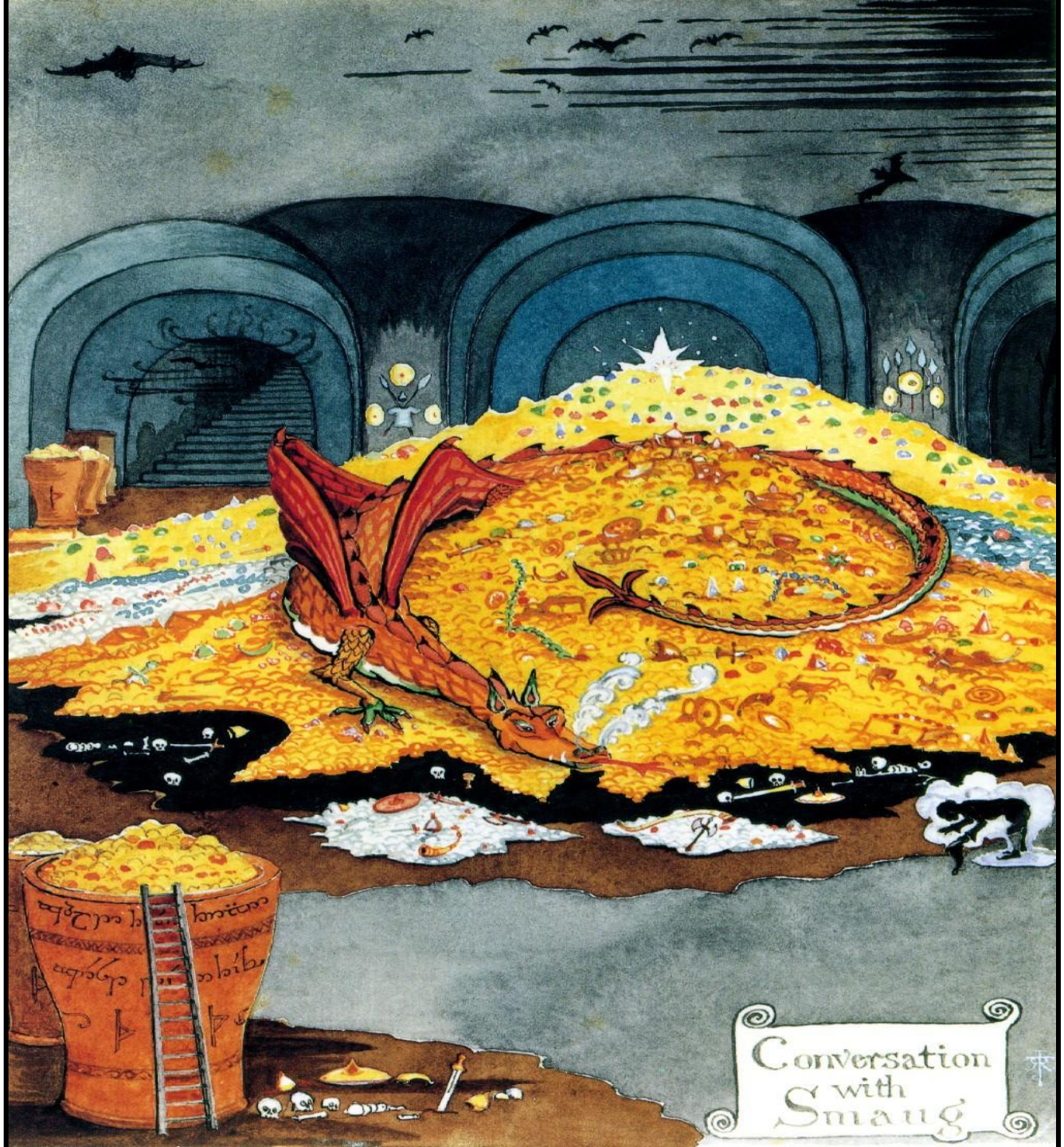


- Pathology departments have little influence on conditions before the tissue reaches them from the endoscopy suite or operating theatre (‘cold ischaemic time’).
- Fixation (preserving), processing (preparing for wax-embedding) and storage arrangements for diagnostic tissue samples vary widely.
- Until recently, getting the best morphology has mattered most.

Is it Actually Any Good?



- A formal biobank aims to standardise cold ischaemia, fixation, processing and storage as far as possible.
- Frozen storage is a particular problem for diagnostic labs but operates well in biobanks – currently a better source for many studies needing high quality DNA and RNA.


Conversation with Smaug

Are Researchers Allowed to Use it?

- Yes…
- …But…

Regulation and Governance

- Research must be of sufficient scientific quality:
  - Peer review and funding
- Research must meet legal requirements:
  - Data protection, GCP, MHRA, HTA etc.
- Research must meet current ethical standards:
  - Research Ethics Committee (REC) review

Data Protection

- Few aspects specific for tissue samples.
- In clinical trials, specific codes will be allocated for anonymity.
- For archived diagnostic specimens, the original laboratory number is sufficient anonymisation.
- Archived microscope slides require de-identification if they carry the patient's name (any new sections cut for research will use number only).

De- and Re-identification

- This can be a nightmare!
- It is easy to deface or obscure the name on a slide label…but…
- If the specimen number is also defaced or obscured, re-identification at the end of the study may be impossible.
- (Original stained sections are usually returned for re-archiving).
- Ideally, peelable, completely opaque labels should be used.

The Human Tissue Act

- In 2004, the government passed the Human Tissue Act.
- The relevant bits for today's discussion came into force in 2006.
- The Act defines what 'human tissue' is (it has to contain cells so, for example, DNA is not tissue).
- The Act regulates the uses to which tissue may be put (so-called 'scheduled purposes') – these uses are not all to do with research.

The Human Tissue Authority

- The Act also created the Human Tissue Authority as the regulatory body to oversee the storage and use of human tissue.
- This body is usually what we mean when we talk about ‘the HTA’.
- The HTA advises individuals and organisations about compliance with the Act and they issue the licenses that allow human tissue to be stored for scheduled purposes.

What is the HTA's Remit in Research?

- Tissue obtained, with specific consent, to be used only for a defined research study, e.g., a clinical trial, is not included.
- But... at the end of the study, if consent is not renewed for additional defined studies, the tissue must be disposed of.
- Unless... the terms of the original or renewed consent include generic consent to store for further, unspecified research.
- This 'legacy' storage requires HTA licensing.

What does HTA Licensing Involve?

- Premises must be fit for purpose (secure and safe).
- Procedures must be fit for purpose (validated, appropriate and documented), from receipt of samples to their disposal.
- Staff must be adequately trained.
- The above applies to the handling of data as well as the samples themselves.
- It must all be auditable - and be audited.

Who is Responsible?

- **Everyone in the research team!**
- A ‘Designated Individual’ is directly responsible to the HTA.
- Additional ‘Persons Designate’ may have specific local responsibilities and report to the DI.
- In many NHS labs, a PD is responsible for research issues; the DI role supports post-mortem requirements of the HTA (which are very different).

Research Ethics Committees - 1

- Organised nationally by NRES, now part of the Health Research Authority (HRA).
- All research involving NHS patients must have a ‘favourable opinion’ from a REC.
- They do not directly assess the scientific merit of research.
- They assess whether proposed research methods are ethically acceptable.

Research Ethics Committees - 2

- They particularly assess the quality of information provided to potential participants.
- They assess whether the consenting process and documents are fit for purpose.
- They are particularly concerned with:
  - Dignity and autonomy
  - The additional burden of research procedures
  - Data security and confidentiality

Research Ethics Committees - 3

- Until recently, their understanding of biosample use, particularly tissue, in research has been poor.
- This is changing...
- HRA/NRES also has an e-mail based, fast-track process for research that raises “no material ethical concerns”.
- The fast track is ideal for anonymous studies of tissue not needing linkage to clinical data.

Is this ‘Red Tape’?

- The HTA and HRA are responsive and flexible even though their processes may seem daunting at the outset.
- Both embrace a fundamental principle of ‘proportionality’ in their oversight.
- There is a third player: R&D departments at Trust level have sometimes been bureaucratic but are improving. Their role is confirming permissions and agreeing logistics. For many, tissue issues are new!

With so much Regulation to Navigate, should Researchers be Worried?

- Not if we embrace the principle of engaging research participants, to obtain and maintain consent.
- Not if we follow the rules, which are reasonable and not unduly burdensome.
- Yes, if we don’t!

Finally… a bit about Consent

- Consent for use of biosamples in research is usually:
  - Specific
  - Generic (and enduring)
  - Tiered
- Generic or tiered consent are needed for biobank storage and (currently unspecified) further use.

Finally… a bit about Consent

- With generic consent, an HTA-licensed biobank can seek generic REC approval for themed research studies.
- (All English, Welsh and NI biobanks are HTA licensed).

Are Researchers Ever Allowed to Use Tissue without Consent?

- It is not essential to have an individual patient's consent to use their 'surplus' archived diagnostic tissue for research.
- However, this research use must be anonymous (not traceable to the individual patient by researchers).
- Ethical approval for the research must be obtained and there are restrictions on the clinical data that can be linked to specimens.
- The supplying pathology department must have an HTA licence.

Some practicalities

- Genuine ‘surplus’ can be ensured for some, larger specimens by taking extra tissue blocks at the outset.
- To speed up later retrieval, these can be flagged in the pathology computer system as ‘available for research’.
- This saves a pathologist having to review all the histology slides to find a suitable block when a research study requires one.

Some practicalities

- Even better, such pre-identified blocks can be handled and stored specifically to maximise research potential (e.g., put in a fridge or freezer long term – this is too expensive to do for all our ‘routine’ blocks).
- Most pathologists are sub-specialised; engage those linked to your MDT to help you with all of this.

The End!