Imperial College London

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The Pathologist's Role in Multidisciplinary Cancer Care Management

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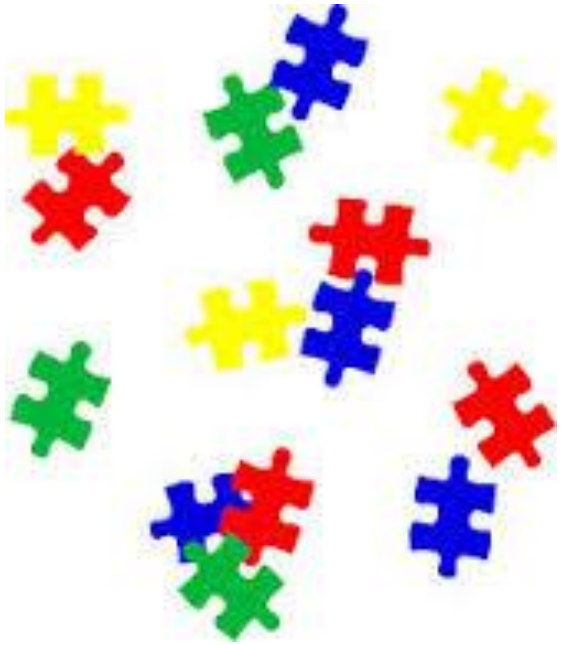
Cancer treatment

- Options and choices are related to:
  - tumour type
  - disease stage
  - cancer biology
  - patient's treatment preferences
  - health status



- Patient and/or clinician goals will change along the course of treatment according to:
  - the relative response of the tumour
  - the patient's health status

The Cancer Patient Care

The care of cancer patients involves the input of a multidisciplinary team comprised of a diverse range of professionals

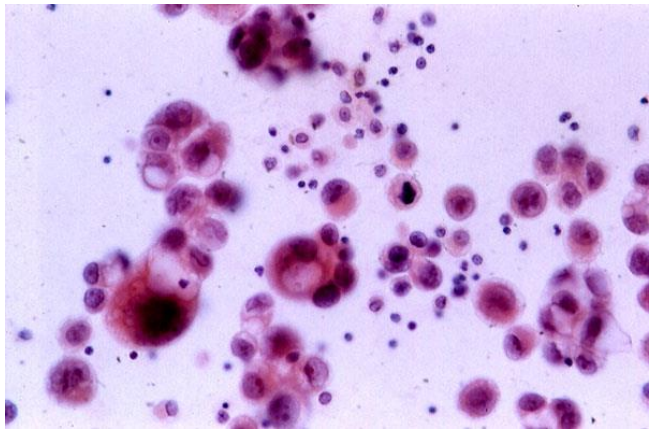
surgeons **oncologists** **radiologists**

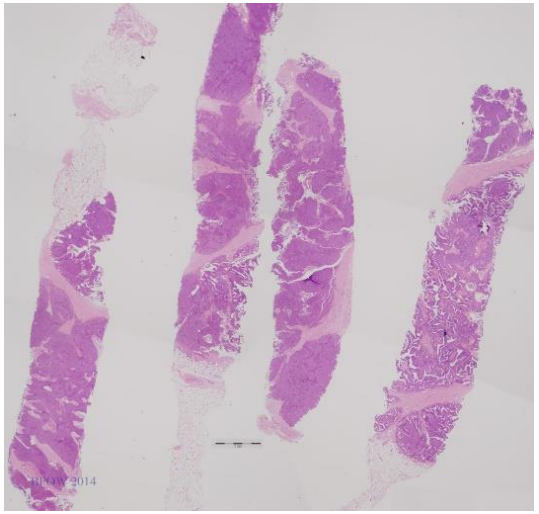
specialist cancer nurses **pathologists**

The role of the pathologist

Initial diagnosis biopsy:

- Cellular pathology confirmation is the unequivocal proof of the presence of a tumour and its nature.
  - Cytology: exfoliative cytology and fine needle aspiration
  - Tissue biopsy





FROM BIOPSY TO HISTOLOGICAL SECTION

biopsy forceps → biopsy on card → cassette

Fix in formalin

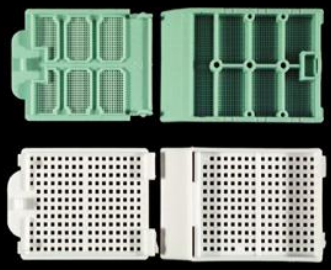
Processing machine

Graded alcohol

Formalin → 70% → 90% → 100% → Xylene → Wax

Embedded in wax block → Sections cut at 3 µm at levels through block → Mounted on slides

Stained with H&E → Coverslip attached → Finished slide



BIOPSY CASSETTES

2

BIOPSY PLACED ON CARD

3

CARD PUT IN CASSETTE

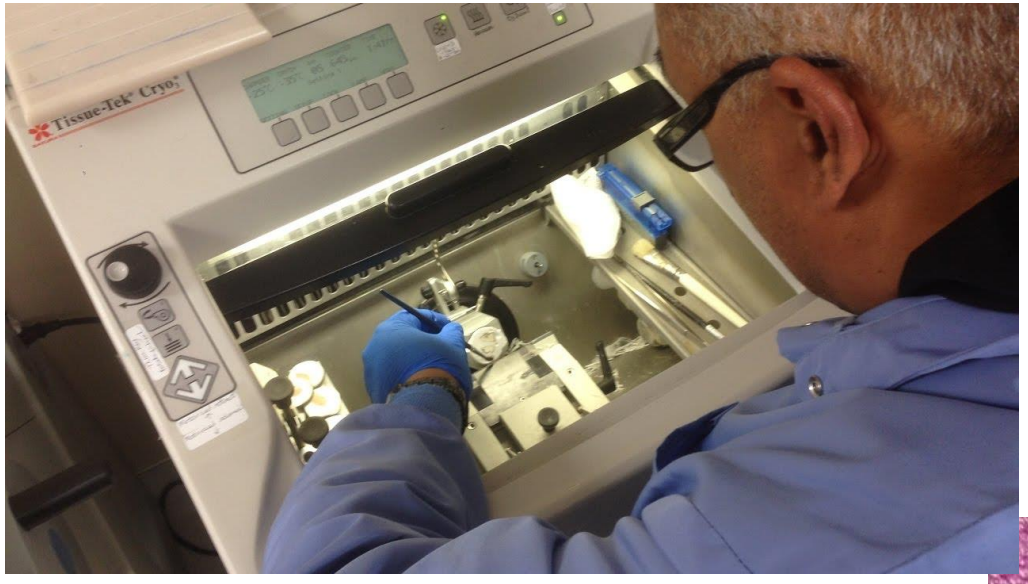
4

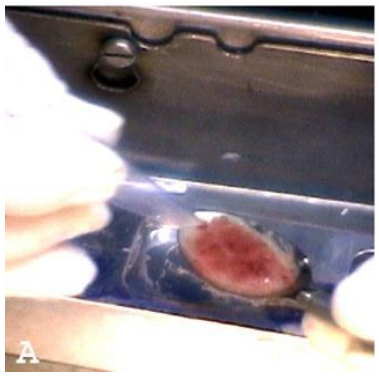
BIOPSY PROCESSED AND EMBEDDED IN WAX ON REVERSE OF CASSETTE

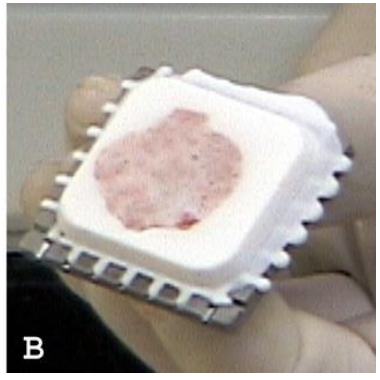
5

SECTION OF BIOPSY STAINED AND MOUNTED

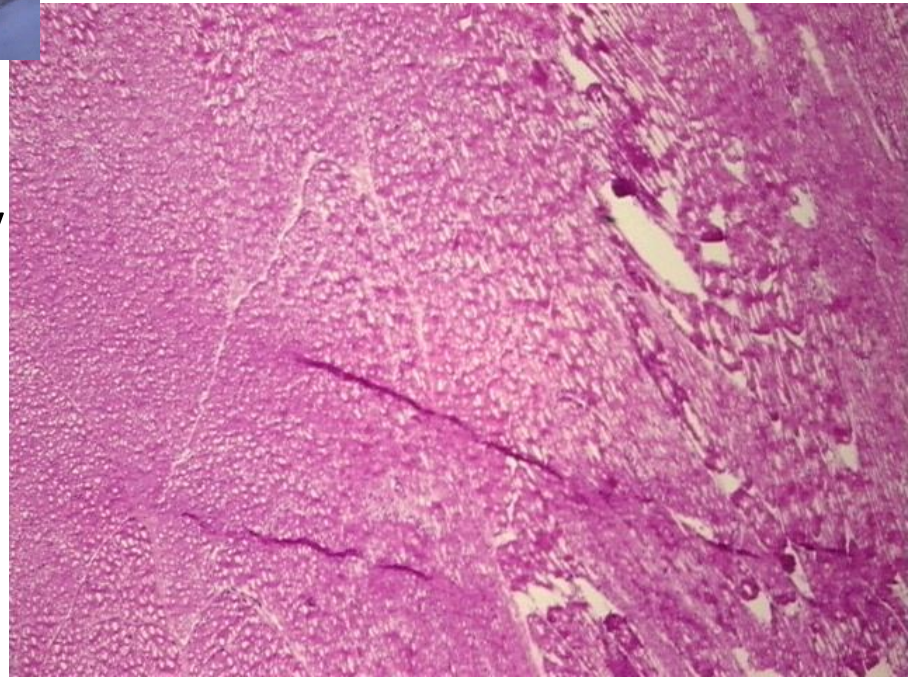
Frozen sections







- Confirmation of diagnosis to guide surgery
- Margin clearance
- Sentinel lymph node

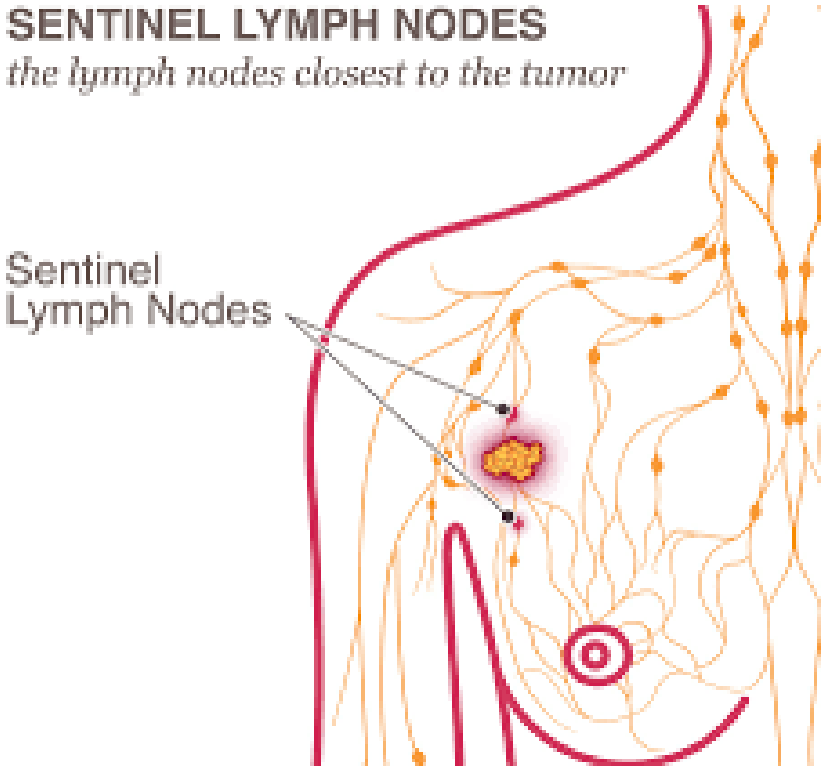


Sentinel Lymph Node

- A sentinel lymph node is defined as " the first node on a regional lymphatic basin that receives lymph flow from a primary the primary tumour.

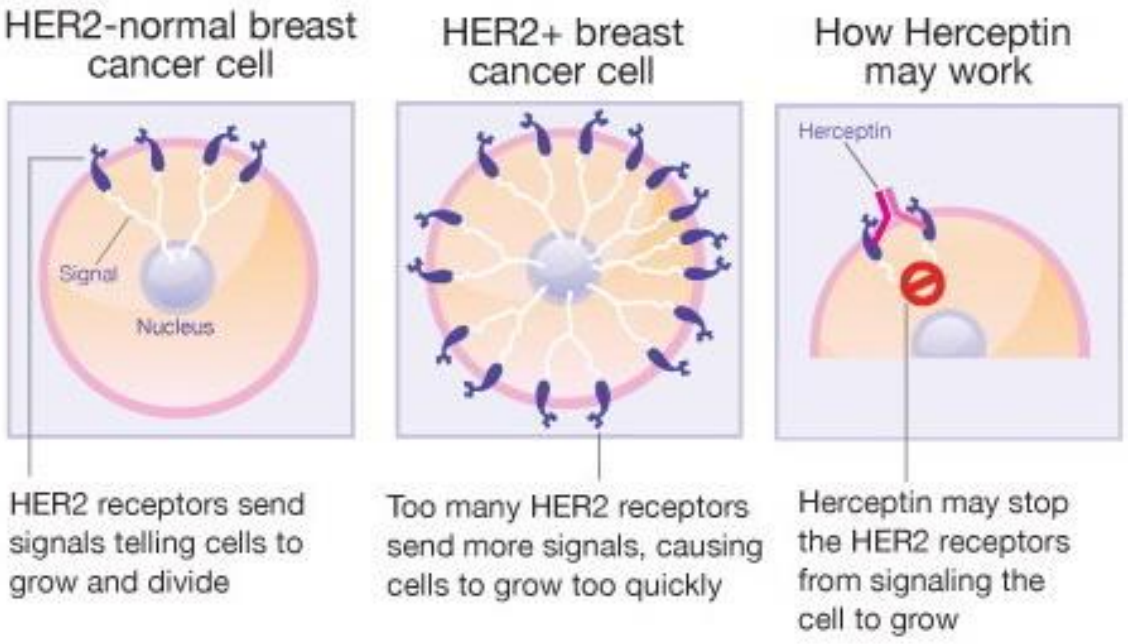
- To avoid the considerable surgical morbidity associated with a full lymph node dissection, biopsy of sentinel nodes is often used to assess the presence or absence of metastatic lesions in the lymph nodes.

- Injection of radiolabeled traces or dyes, and examination of the sentinel lymph node during surgery can guide the surgeon to the appropriate therapy.



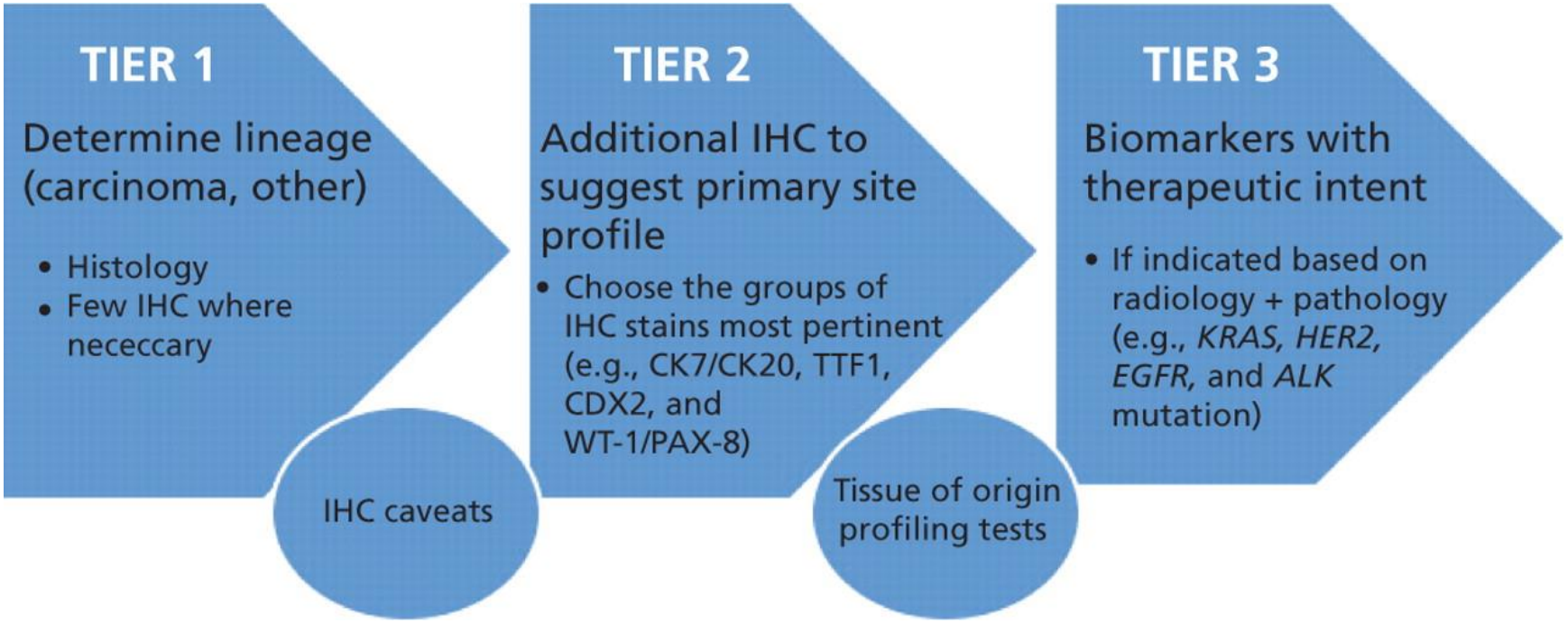
Significance of primary diagnosis of known primary site at presentation

- Guidance for treatment plan: surgery, chemotherapy, neoadjuvant therapy
- Prognostic factors: disease free survival and overall survival
- Data for targeted therapy: e.g. eligibility for Herceptin therapy in breast carcinoma



Significance of primary diagnosis of unknown primary site at presentation "CUP"

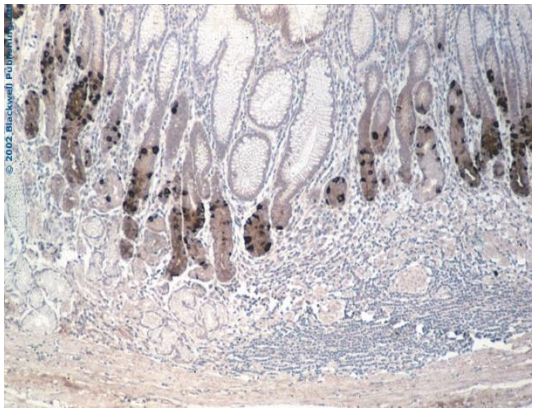
- In tumours presenting with metastasis if the primary site of origin is not apparent on imaging pathologists can help in identification of primary site of origin.



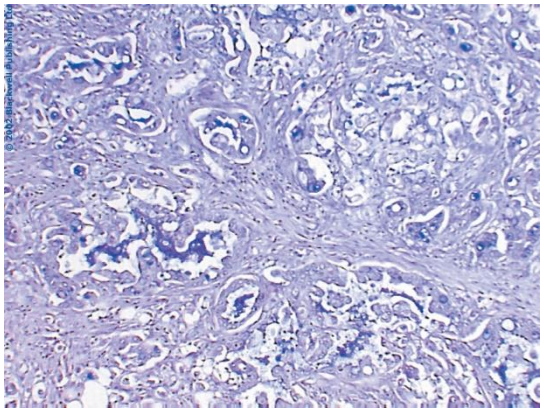
Chemsitry

Special stains

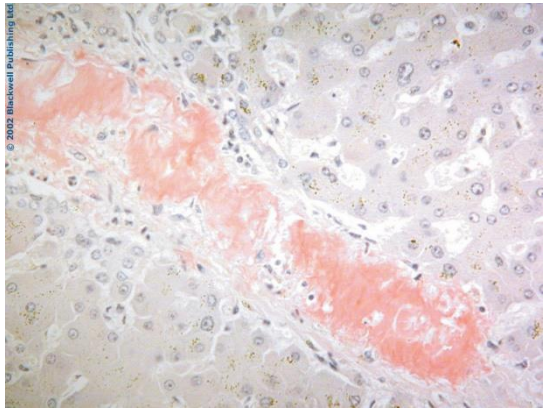
- Alcian blue
- Periodic acid schiff
- Masson Fontana
- Grimeleus
- Phosphotungestic acid haematoxylin
- Mucicarmine



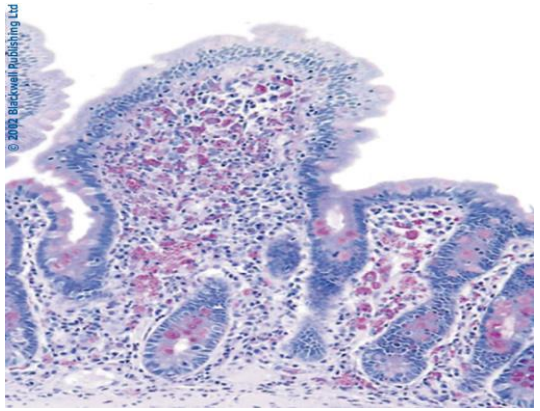
Grimeleus



Alcian blue



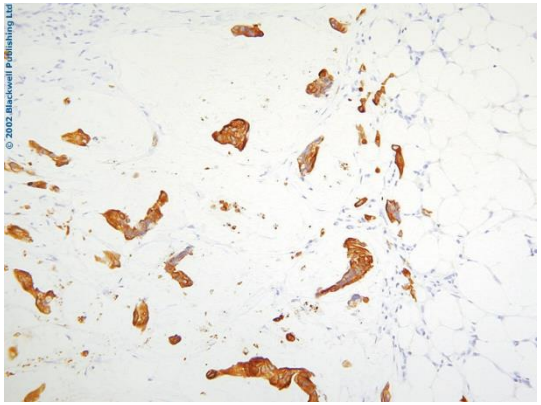
Congo red



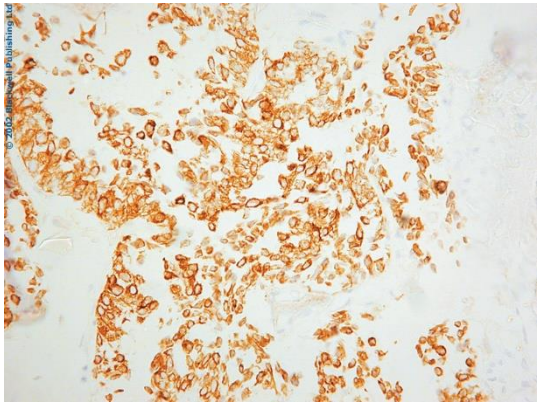
PAS

Carcinoma of unknown primary

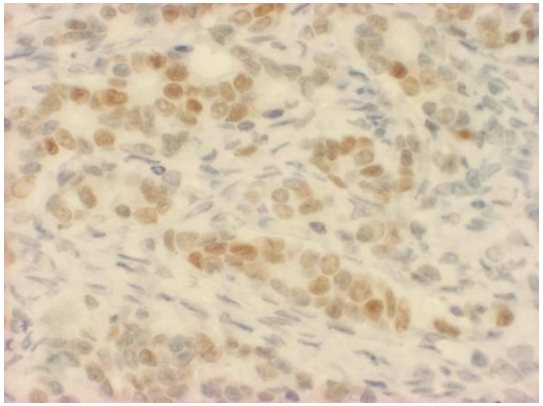
- CK 7, CK 20: cytokeratin profile
- Ca125: is positive in gynaecologic cancers and also breast, colon, lung and pancreas
- Hormone receptors: gynaecologic cancers and breast
- GATA-3 & GCDFP-15: positive in most breast



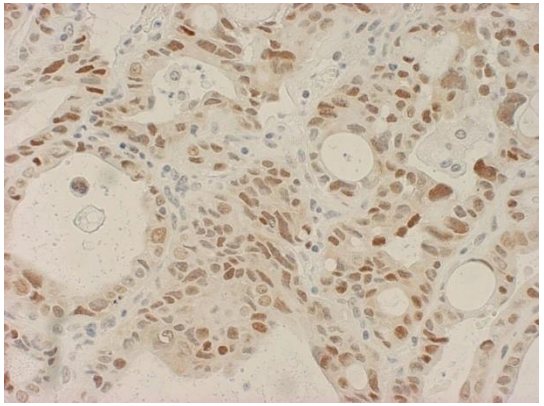
CK20



CK7



ER



P53

Reporting on the resection specimen

- Tumour type, grade and stage.
- Completeness of excision
- Prognostic data
- Data for targeted therapy
- Data to decide on merit of inclusion into clinical trials

Follow up

- Histological confirmation of tumour recurrence

Clinical Trials and Original Research

Clinical trials

- Trial design
- Tissue for translational research

Original research studies

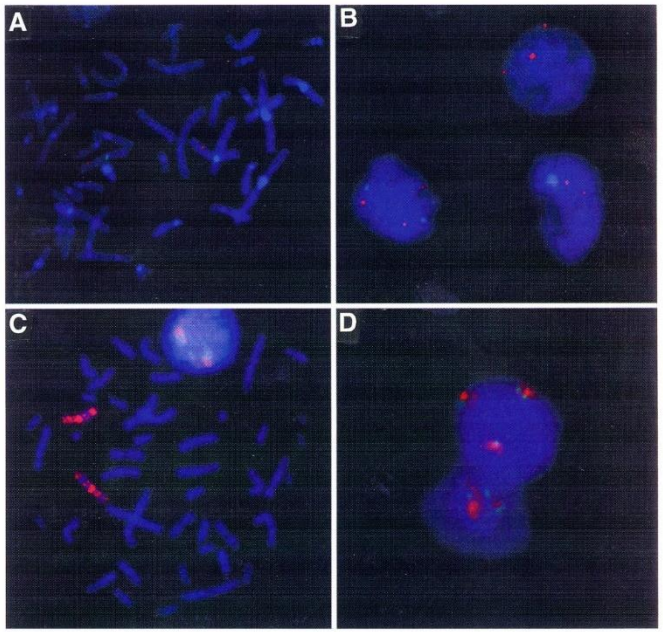
- Design
- Choice of cases
- Reading and interpretation of results

Molecular Profiling

- Useful in molecular stratification of otherwise identical tumours or those of distinct histogenesis that share a mutation for the purpose of targeted treatment and prognostication.

Molecular Profiling may be High-throughput and targeted.

- DNA:
  - Mutation analysis: e.g. Direct sequence, Sequenom
  - Gene amplification: FISH
  - Chromosomal aberrations: e.g. aCGH, FISH
  - Gene methylation: e.g. pyrosequencing
- RNA: In Situ Hybridisation, gene expression arrays
- Proteins: Immunohistochemistry, proteomics



Trisomy 7 in hereditatry papillary RCC

Zhuang Z et al. Nat. Genet, 1998

Is the development of omics the end of histopathology?

- Histopathologic inspection of tumours also provides information about other important characterisitcs such as grade, invasiveness and tumour heterogeneity.

- Different cancers may harbour the same molecular change, and hence be amenable to targeted therapy.

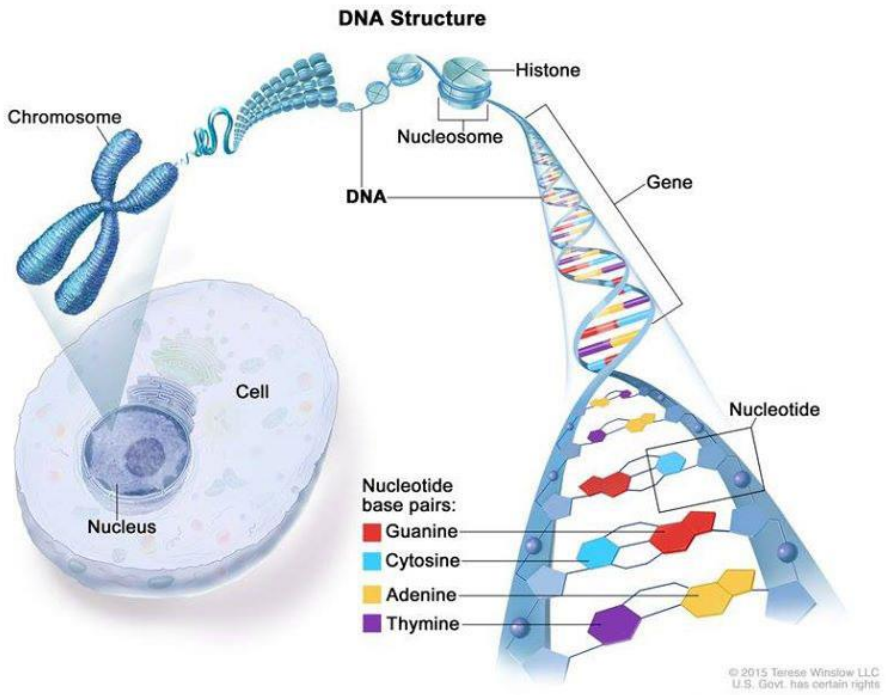
e.g. BRAF inhibitors (BRAFomas). However, different types of tumours respond differently.

  - Hairy cell leukemia appear to have sustained responses
  - Melanomas respond transiently
  - Colon carcinomas respond little if at all.

The most accurate diagnosis and assessment of prognosis in cancer patients will be arrived at by a combination of morphologic histopathological assessment and molecular techniques

Identification of patients with hereditary cancer syndromes

Approximately 5–10% of all cancers occur in patients with hereditary cancer syndromes



Patients with hereditary cancer syndromes are at risk for additional malignancies following their first diagnosis

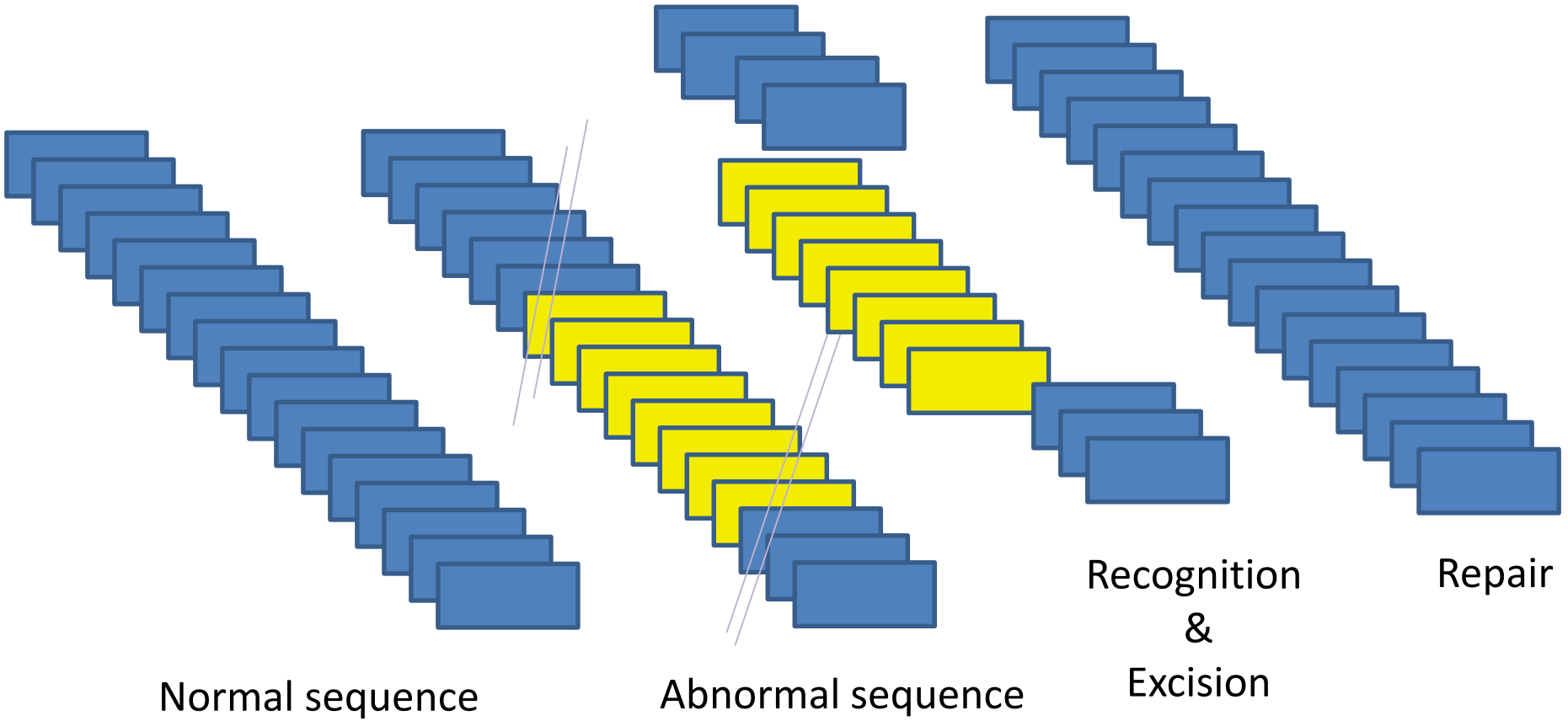
Early identification of these patients after an initial cancer diagnosis is the key to implementing cancer risk-reducing strategies

Identifying a hereditary syndrome is important for relatives, who are at a high risk for harbouring a mutation

Lynch Syndrome

- One of the most common hereditary cancer syndromes is Lynch syndrome (LS).
- Accounts for up to 4 % of all colorectal cancers (CRC) and it is the most common hereditary CRC predisposition syndrome.
- In patients with early-onset CRC this number can be up to 17%.
- An autosomal dominant genetic disease caused by germline mutations in mismatch repair genes, MLH1, MSH2, MSH6 and PMS2.

Mismatch repair system



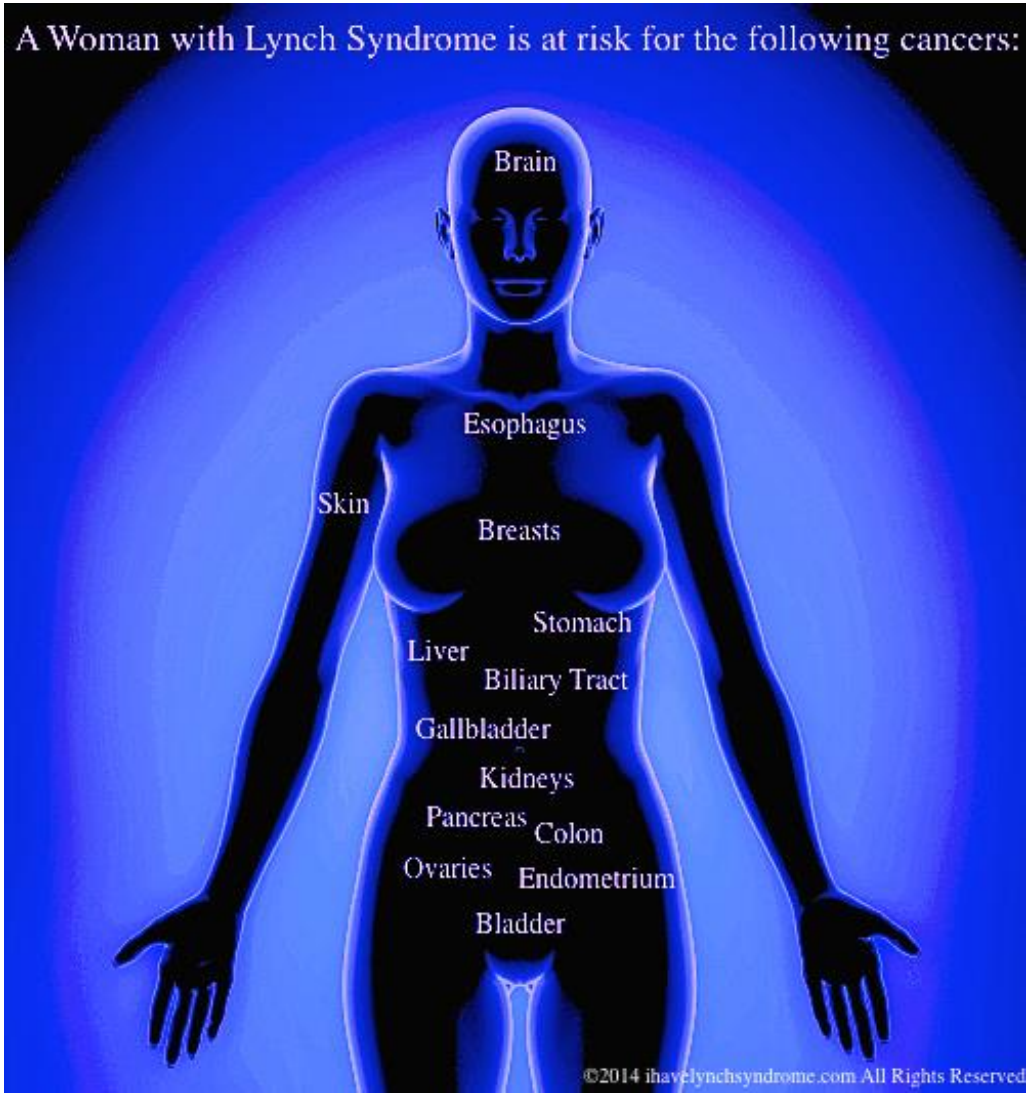
Mutation leads to the accumulation of DNA errors in microsatellite regions - repetitive areas in the DNA

Lynch Syndrome – The spectrum

- COLORECTAL CANCER
- ENDOMETRIAL CANCER

- urinary tract
- ovary
- stomach
- small intestine
- hepatobiliary tract
- brain
- skin

- unusual tumors:
  - prostate cancer
  - breast cancer
  - lung cancer
  - adrenal cortical neoplasm
  - mesothelioma
  - pancreatic acinar cell carcinoma
  - pancreatic neuroendocrine tumor
  - some sarcomas



Levels of evaluation for the diagnosis of a hereditary tumour syndrome

- Patient / family history and clinical criteria
- Histological confirmation of tumour type and features
- Tumour tissue testing
- Genetic testing

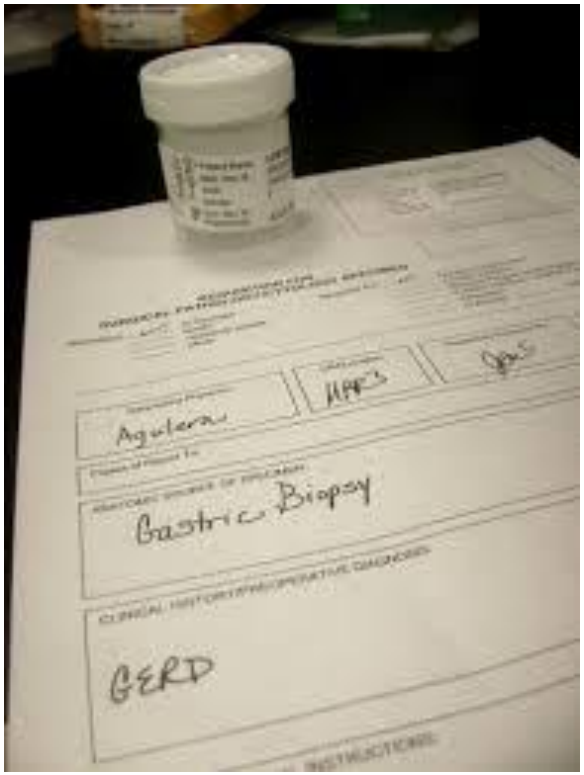
Detection of a
pathogenic germline gene mutation
is the definitive criterion for
diagnosis

Pathologists play an important role in the management of LS

Histologic features over-represented in microsatellite instable cancers

Referral clinical information

- LS is characterized by:
  - an earlier age of CRC diagnosis(45 vs 64 years)
  - likely to have multiple synchronous or metachronous tumours

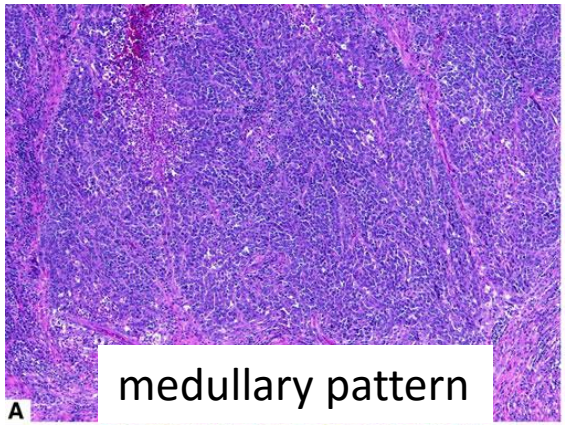


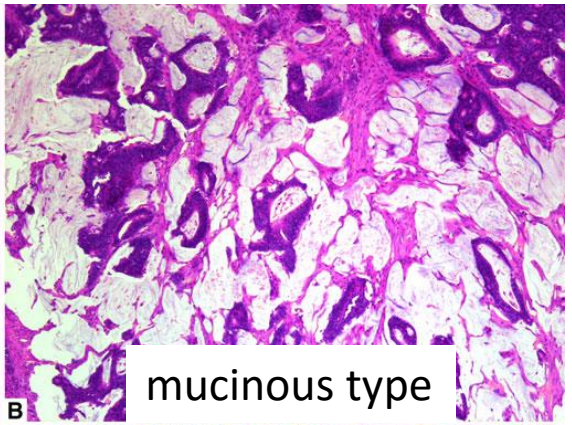
Specimen evaluation

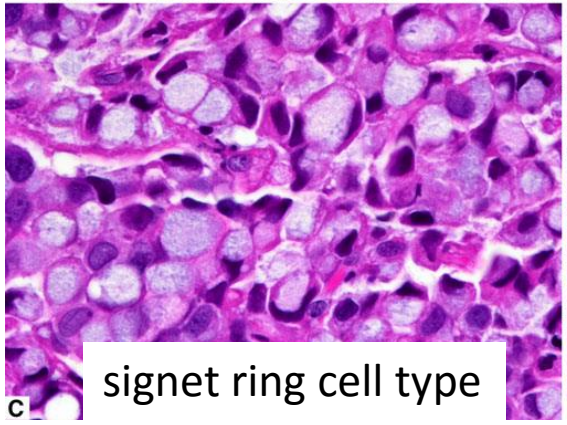
Gross:
Right sided predominance
Exophytic growth pattern
Large size

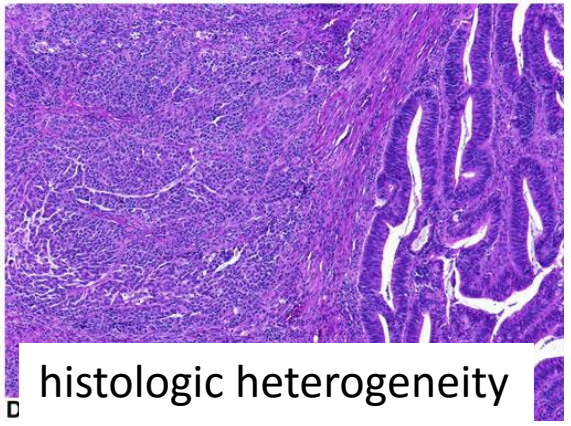
Microscopic:
Poor differentiation
Medullary growth pattern
Mucinous / signet ring
Peritumoral Crohn's-like lymphoid reaction.

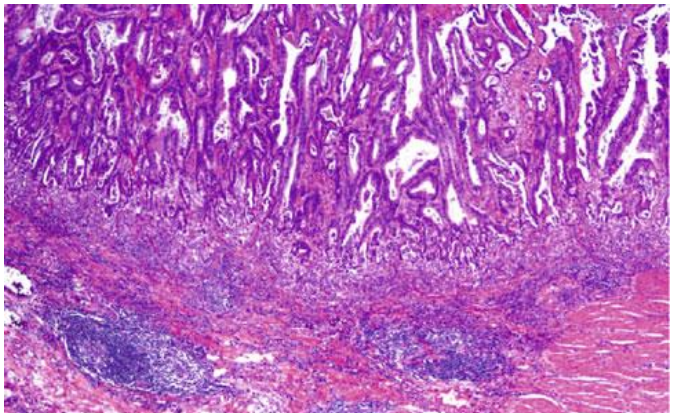
Tumor heterogeneity
Lack of tumor budding







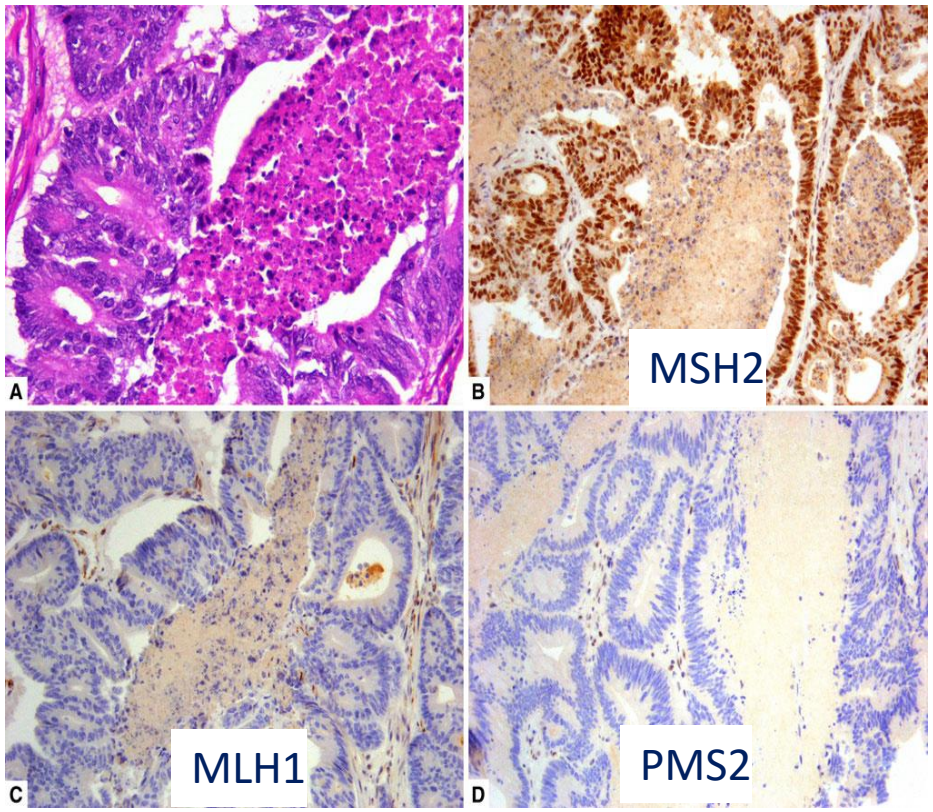




Peritumoral Crohn's-like lymphoid reaction

Immunohistochemistry

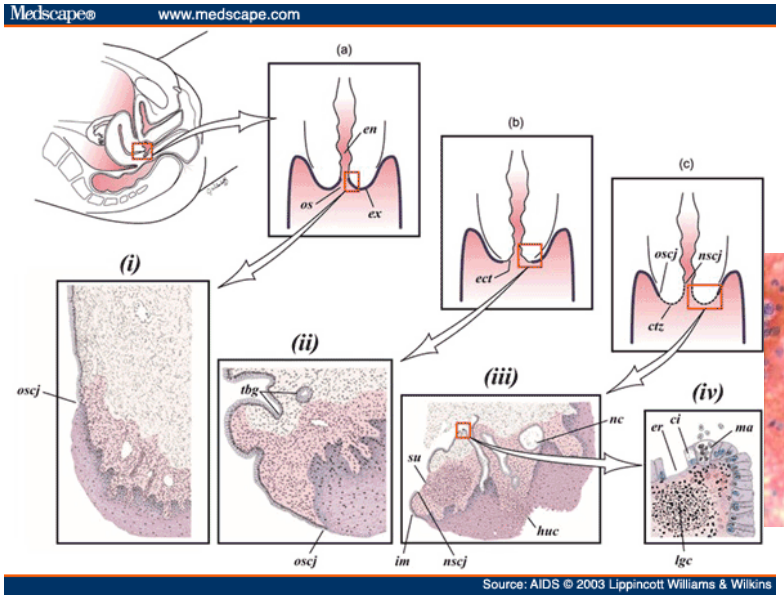
- There are immunohistochemical antibodies available for the four mismatch repair proteins, MLH1, MSH2, MSH6 and PMS2.
- One or two of the proteins is absent in 83% of tumours from individuals with LS.
- This indicates which gene should be targeted for germline genetic testing.

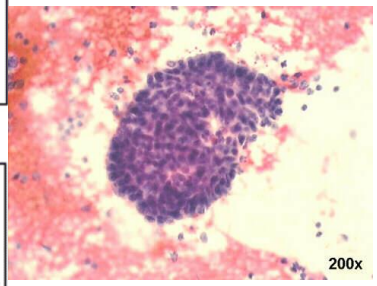


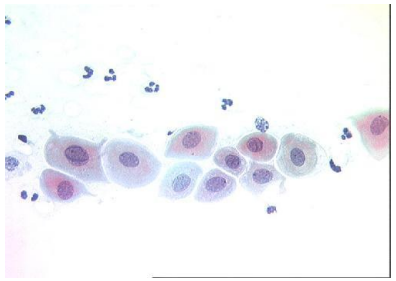
- The pathologist's role is:
  - primarily by information gained from tumour histopathology
  - DNA mismatch repair protein immunohistochemistry
  - tissue selection for MSI-PCR testing
  - guidance to which gene to be tested for mutation

Cancer screening programs

- **Breast screening** is offered to women aged 50-70.
- **Cervical screening** is offered to women aged 25-64.
- **Bowel screening** is offered to men and women aged 60-74.







- Cancer services in the UK in the early 1990s were far from satisfactory.
- There were gross variations in clinical practice.
- Government: ‘A strategic framework to help providers of cancer services to make well informed and wise decisions’.
- One of the means chosen to instantiate this, articulated in the Cancer Plan of 2000, was the MDT meeting.

The Multidisciplinary Team

The MDT meeting can be defined as a regularly scheduled discussion of patients, comprising professionals from different specialties

- The role of the MDT meeting was primarily educational.

- Now mandatory that all cancer patients cared for in public hospitals are discussed and treated by a MDT.

- Platform for consultation amongst professionals in a single setting to formulate treatment recommendations providing high-quality care.

MDT Meeting

- Coordination of care within the team ensures
  - accurate staging
  - consideration of different treatment options
  - continuity of treatment
  - appropriate follow-up

- Between 4% and 35% of patients discussed had changes to diagnostic reports:
  - stage
  - primary site of tumour
  - histology
  - pathological grade

Infrastructure for meetings

A- Physical environment of meeting venue:

- Dedicated MDT room if possible

- Room is appropriate in size and layout
  - all team members have a seat
  - are able to see each other
  - are able to view diagnostics

The 

Membership and attendance

- For effective decision-making all relevant professions/disciplines
  - represented
  - in attendance

surgeons **oncologists** **radiologists**

specialist cancer nurses **pathologists**

Diagnosis of screen detected and symptomatic Breast lesions

Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening

June 2016, RCPath

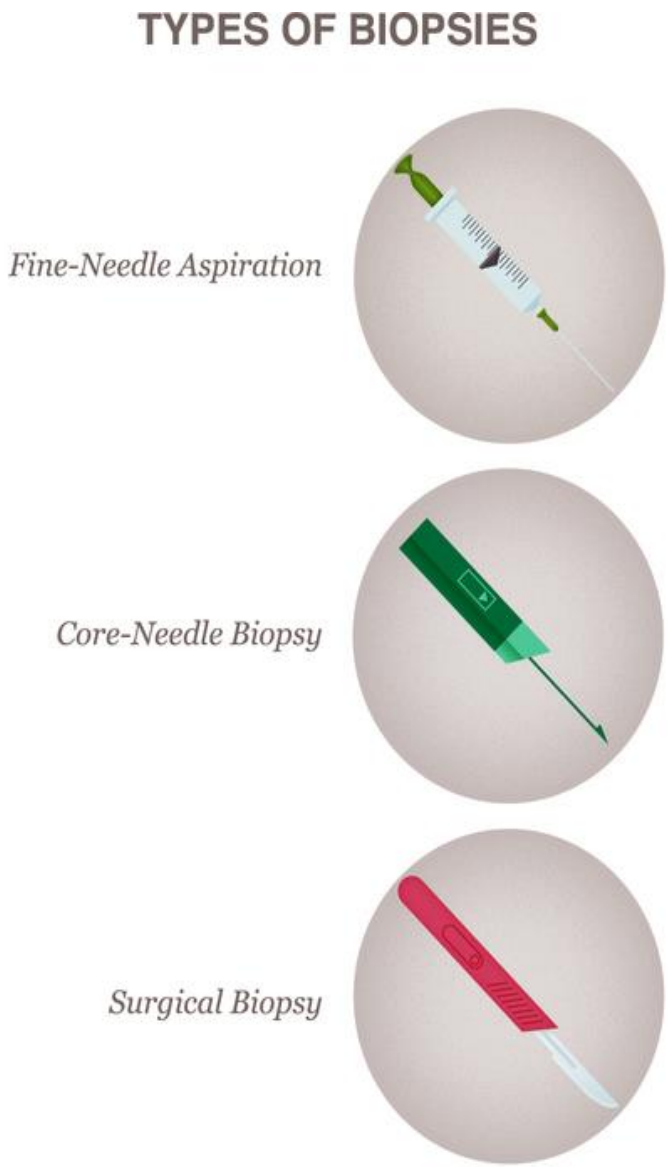
All

screening or symptomatic detected abnormalities must be discussed at a multidisciplinary meeting where findings from all modalities are reviewed and further management is decided accordingly

Before Biopsy

- For certain types of mammographic abnormality e.g. low level suspicion microcalcification, a larger volume of tissue is required for accurate diagnosis.

- Consideration of the likely nature of the lesion from the imaging features should be taken into account when deciding on the sampling method to be used.
  - Gauge of needle
  - Image guidance



After biopsy

- Histological examination of core biopsy samples is performed to give a pathology category classification (B1–5).

- The MDT meeting judges whether the biopsy is concordant with radiological and clinical findings and is representative of the lesion.

- If a biopsy is for investigation of calcification, the presence of microcalcification in the biopsy contributes to the discussion about whether the sample includes the desired lesion and informs assessment of adequacy of the biopsy.

- Discussion of the options for neo-adjuvant therapy.

After surgery

- Discussion of further management based on results of the surgical specimen.

- A decision must be reached as to whether
  - the histological findings of the core biopsy have been appropriately interpreted
  - the appropriate area of lesion has been removed in the surgical specimen
  - there is possibility that the lesion remains in the breast

Era of personalised medicine

- The MDT meeting provides a forum in which clinical evidence combines with individual patient data to create a personalized treatment plan.

- Choice of targeted therapies and clinical trials necessitates the presence of MDT decision based on accuracy of information and knowledge of available choices.

The merits of being in the same room

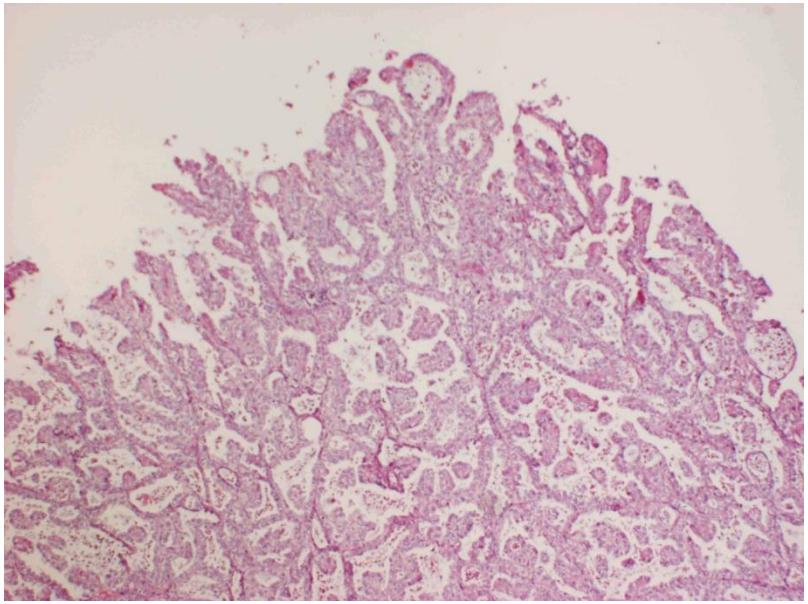
Clinical History

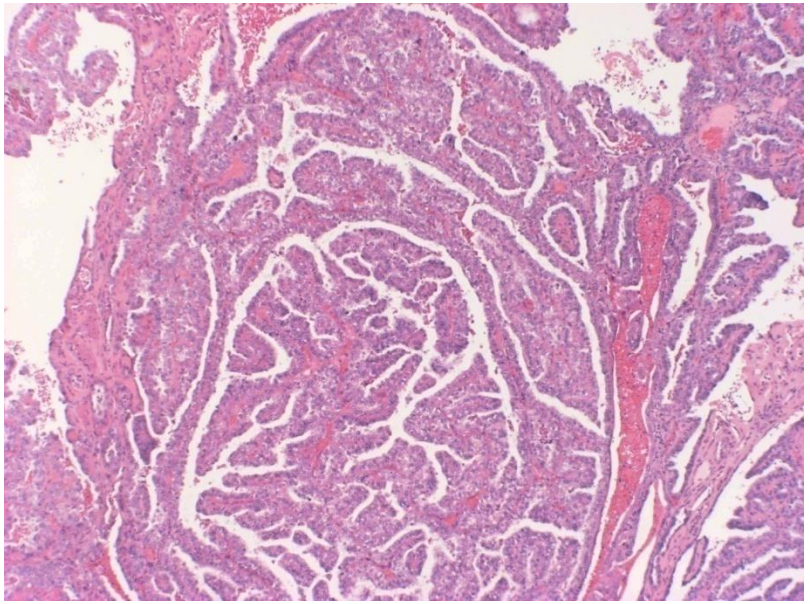
- 70 year old female
- Had a distended abdomen
- No other lesions
- Endometrial biopsy: Endometrial high grade carcinoma
- TAH and BSO for endometrial carcinoma

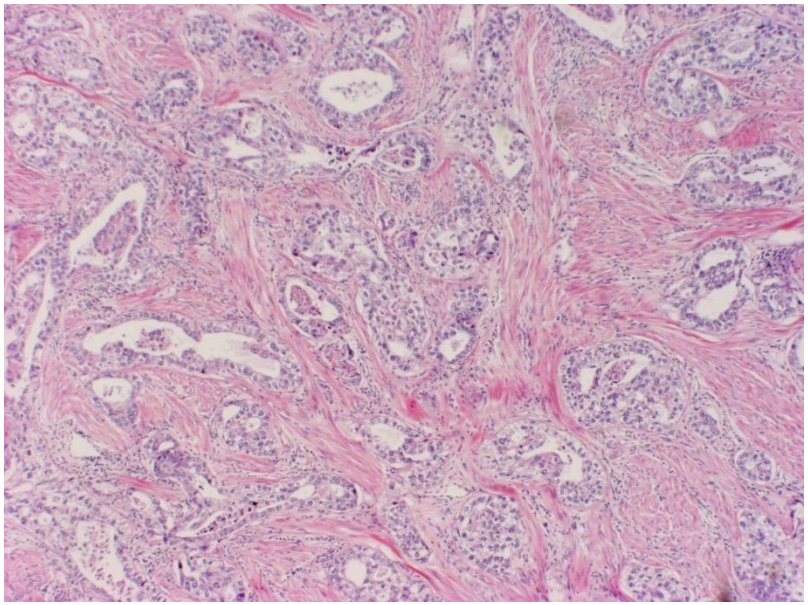
Macroscopy

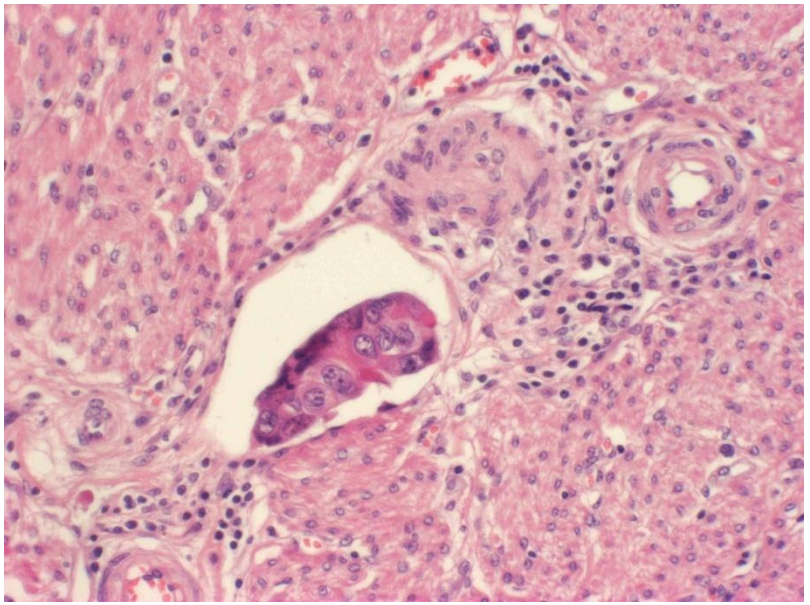
- Polypoid mass in uterine cavity
- Ovaries: Normal size and appearance
- Fallopian tubes: Normal

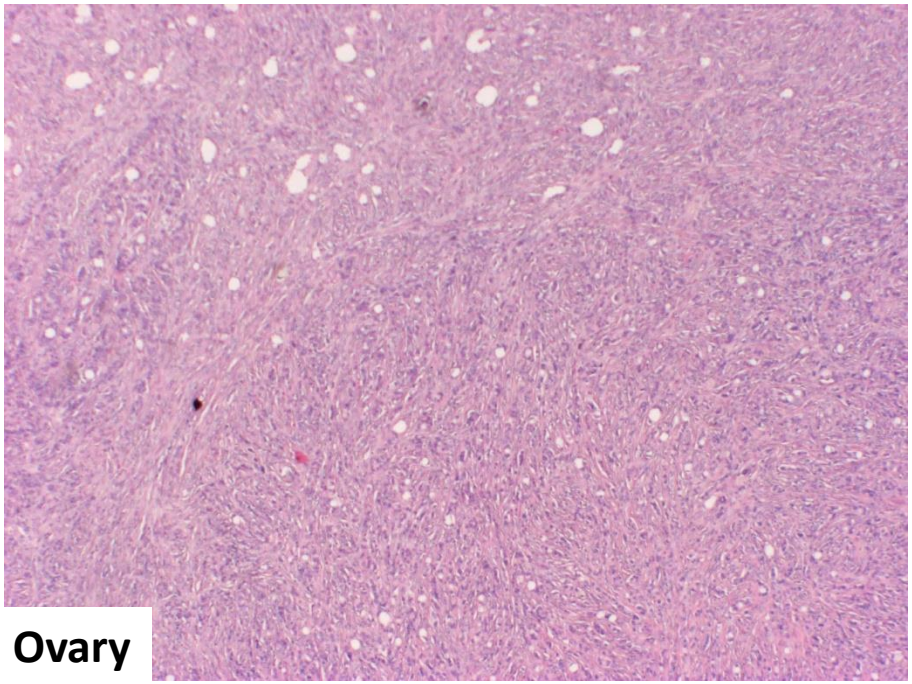
Uterine tumour



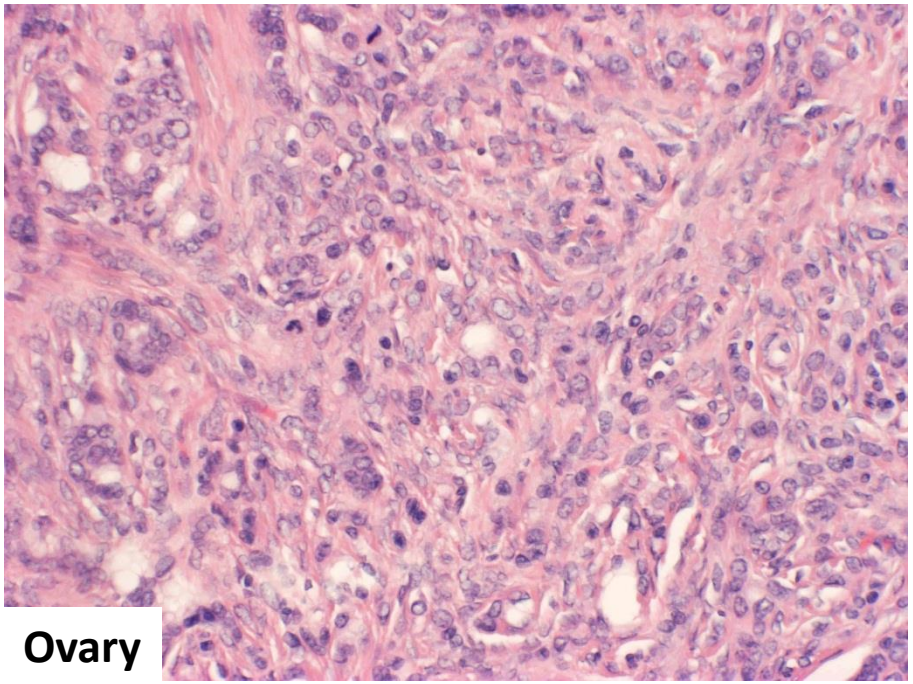




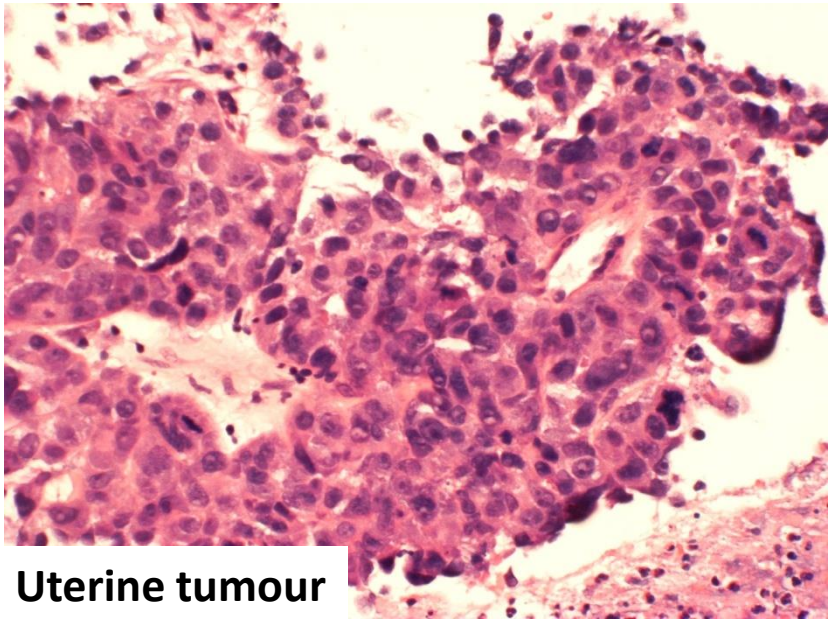




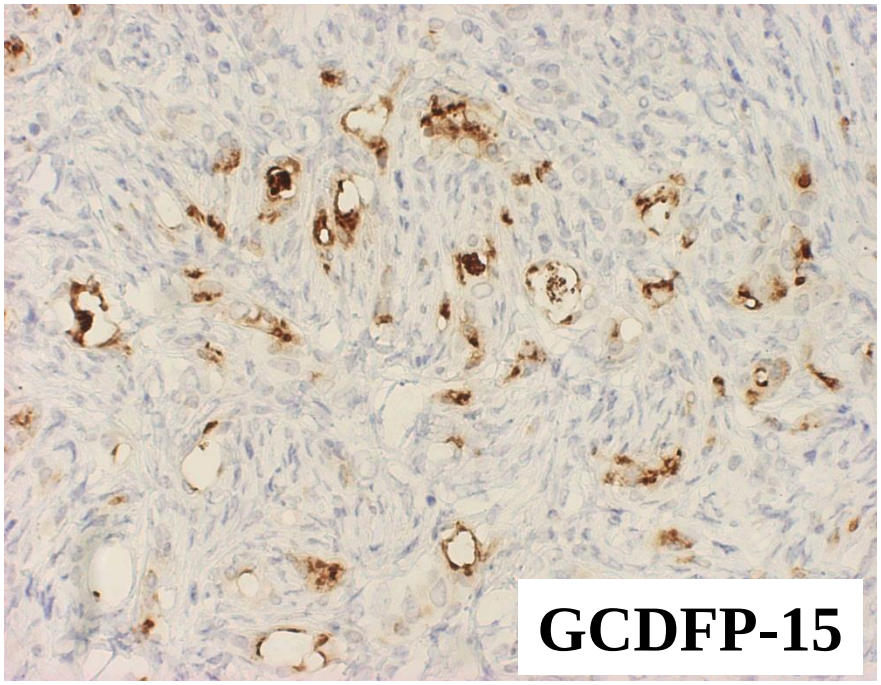
Ovary

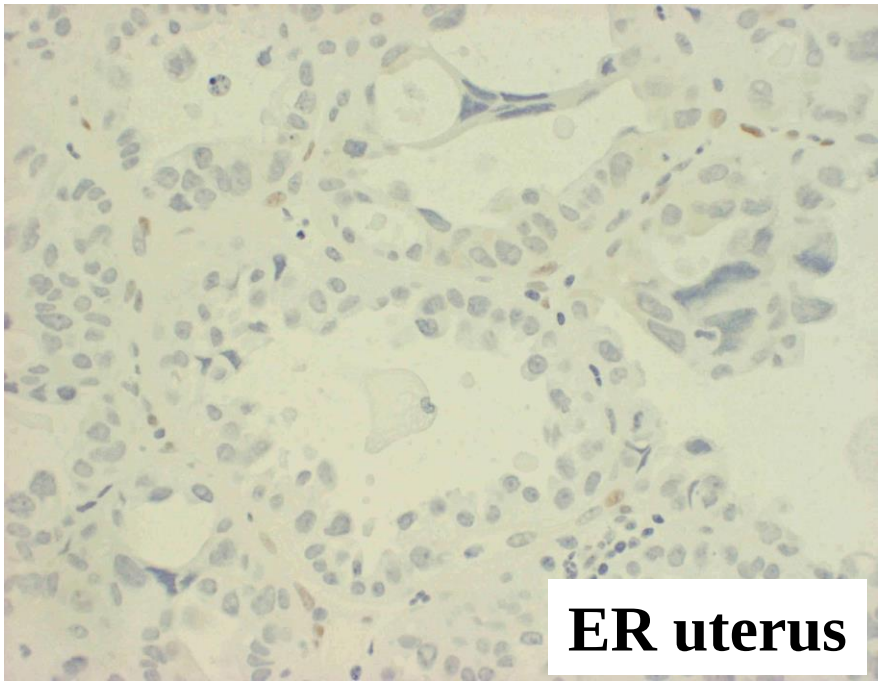


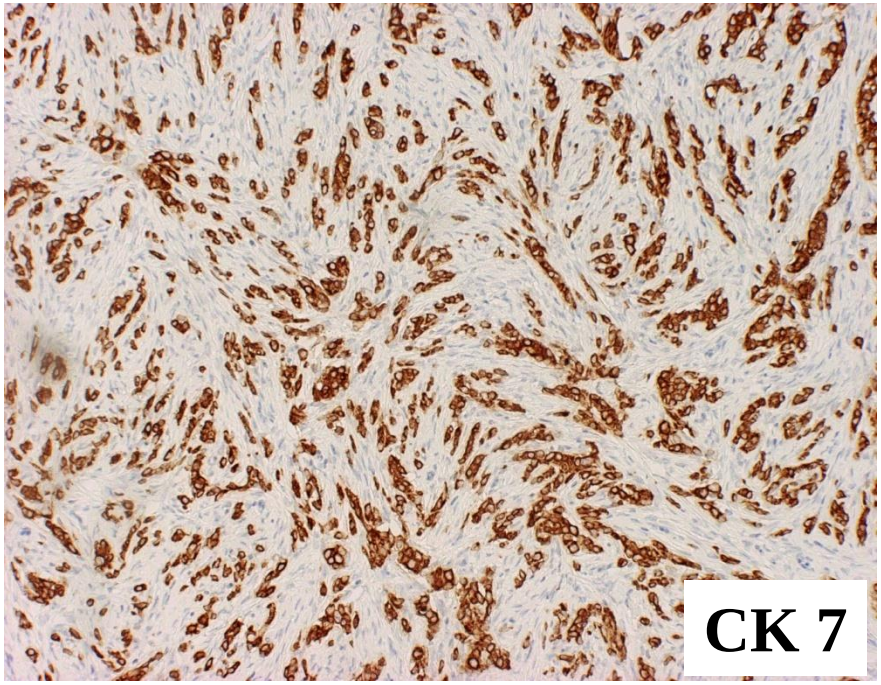
Ovary

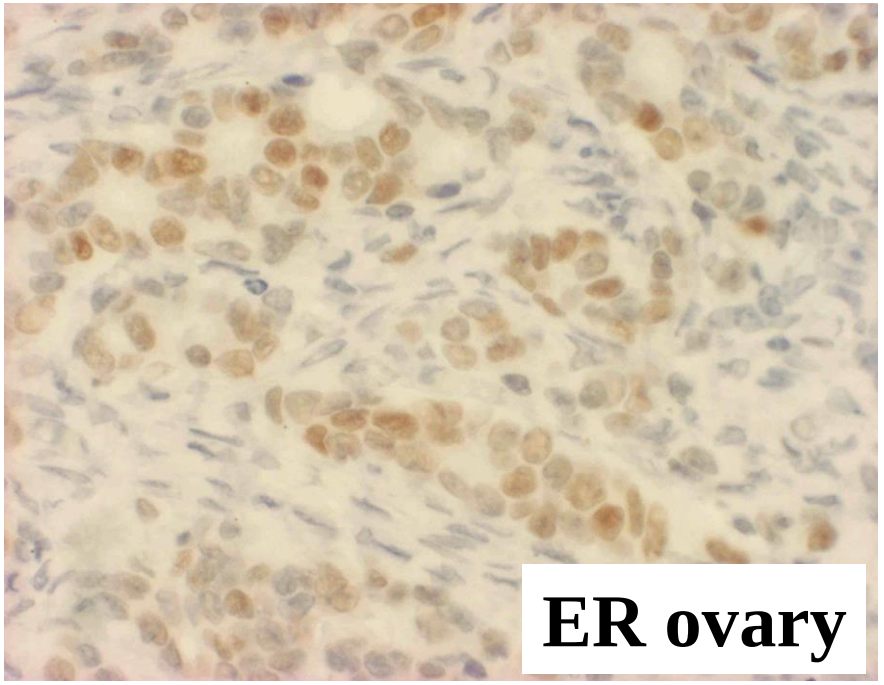


Uterine tumour


GCDFP-15


ER uterus


CK 7


ER ovary

A fully informed decision on treatment

delayed by 1-2 weeks

is clearly preferable to rushed time target-driven decisions made without the patient being offered a fully informed choice as ratified by a multidisciplinary team

Eur J Surg Oncol. 2016 Jul;42(7):994-8.
Viewpoint: Availability of oestrogen receptor and HER2 status for the breast multidisciplinary meeting discussion; time to get it right.
Francis A, et al

Whilst the early anxiety of waiting for all relevant information to be available may be stressful for patients,

not being sure that they have been offered fully informed treatment choices is also stressful

and could cause longer lasting anxiety

both during and after treatment

Eur J Surg Oncol. 2016 Jul;42(7):994-8.
Viewpoint: Availability of oestrogen receptor and HER2 status for the breast multidisciplinary meeting discussion; time to get it right.
Francis A, et al

The Multidisciplinary Team

Ideally get together in the same room regularly

What do clinicians expect from Pathologists??

- Diagnosis
- Prognosis
- Profiling that may influence therapy

What do pathologists need from clinicians??

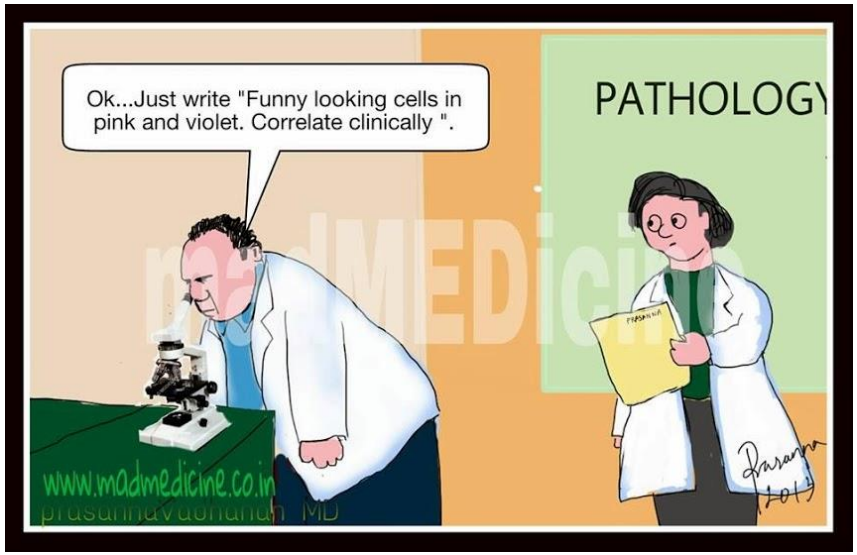
Complete relevant information

Timely and effective communication

The pathologist?

Radiologist

Surgeon



Oncologist

Cancer Nurse

Members of other MDT

Pathologists are uniquely positioned with an overview of a patient's illness and have a responsibility to use this position to direct care to the best of their abilities