Quality assurance and quality control in pathology in breast disease centers

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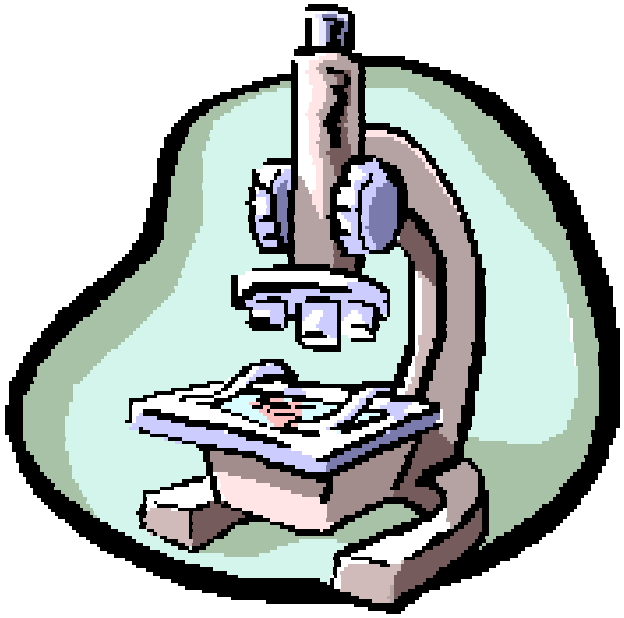
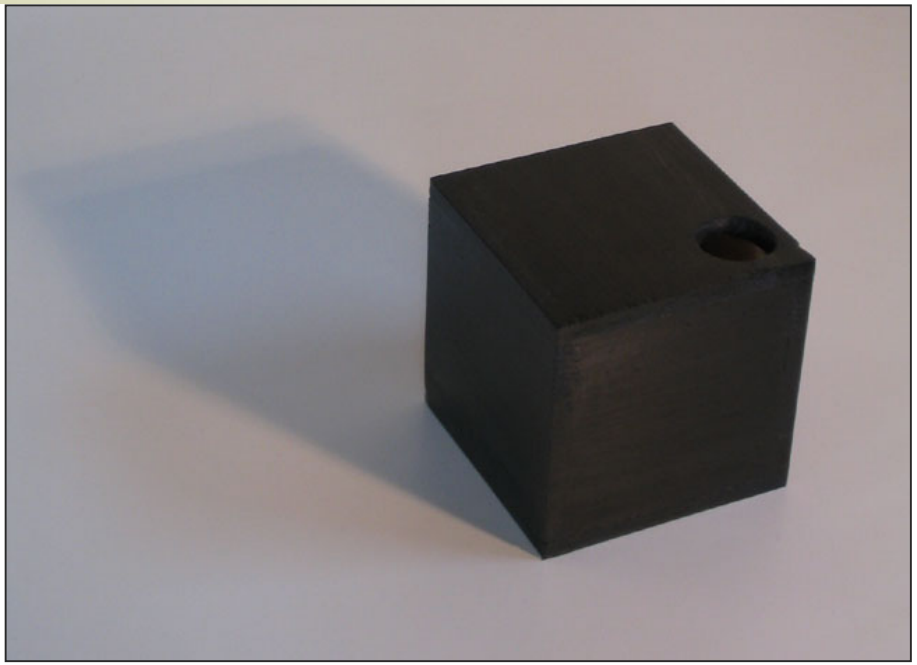


- Breast disease centers were created in order to deliver the best possible service to breast cancer patients.
- In order to achieve this, each sub-unit of the center has to undergo a strict improvement program with continuous monitoring.
- All Breast disease center sub-units have to perform “cross talking”.

Pathology as a black hole

Or maybe a black box as viewed by many…



When actually it is of course…

A **personalized consultation** rendered by highly qualified medical practitioners and enabled by a close contact with the relevant clinicians.

- Pathologists have to move from the field of diagnosis and classification only.
- The field of **molecular oncology** must be **adopted** by us the pathologists and should not be left to drift to other specialties.
- Any **tissue based investigation** will always be done better by pathologists.
- These investigations may also assist in diagnosis and classification of cancer in the future .

Evolution of Pathology

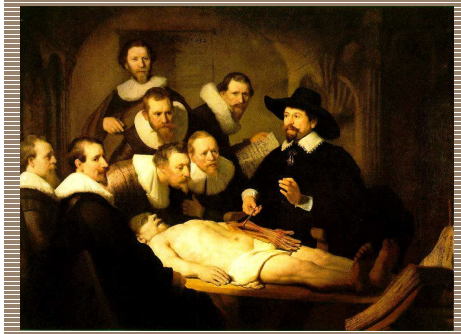
Gross Pathology

Antonio Benivieni (1443-1502): First autopsy

Giovanni Morgagni (1682-1771): Correlated patient symptoms to autopsy findings

John Hunter (1728-1793): Devised method for preserving tissue

Bichat (1771-1802): "Father of modern pathology"



Cellular Pathology

Leeuwenhuek (1858-1950): Developed 1st microscope

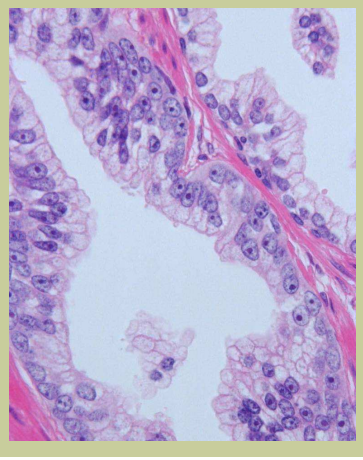
Virchow (1821-1905): Recognized that diseases arise from alterations within tissues and cells

Morphologic Pathology

Morphologic classification of cancer

Pathologists provide diagnostic and prognostic information

Hematoxylin and eosin is 'primary stain' for all cases

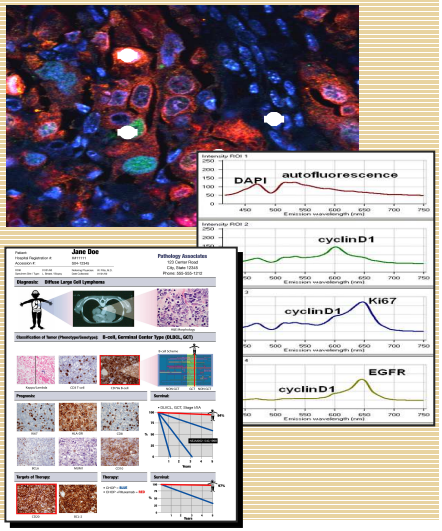


Molecular/Predictive Pathology

Comprehensive molecular tumor profiling

Pathologists provide personalized medicine /predictive biomarker information

Proteomic and genomic data in the context of morphology

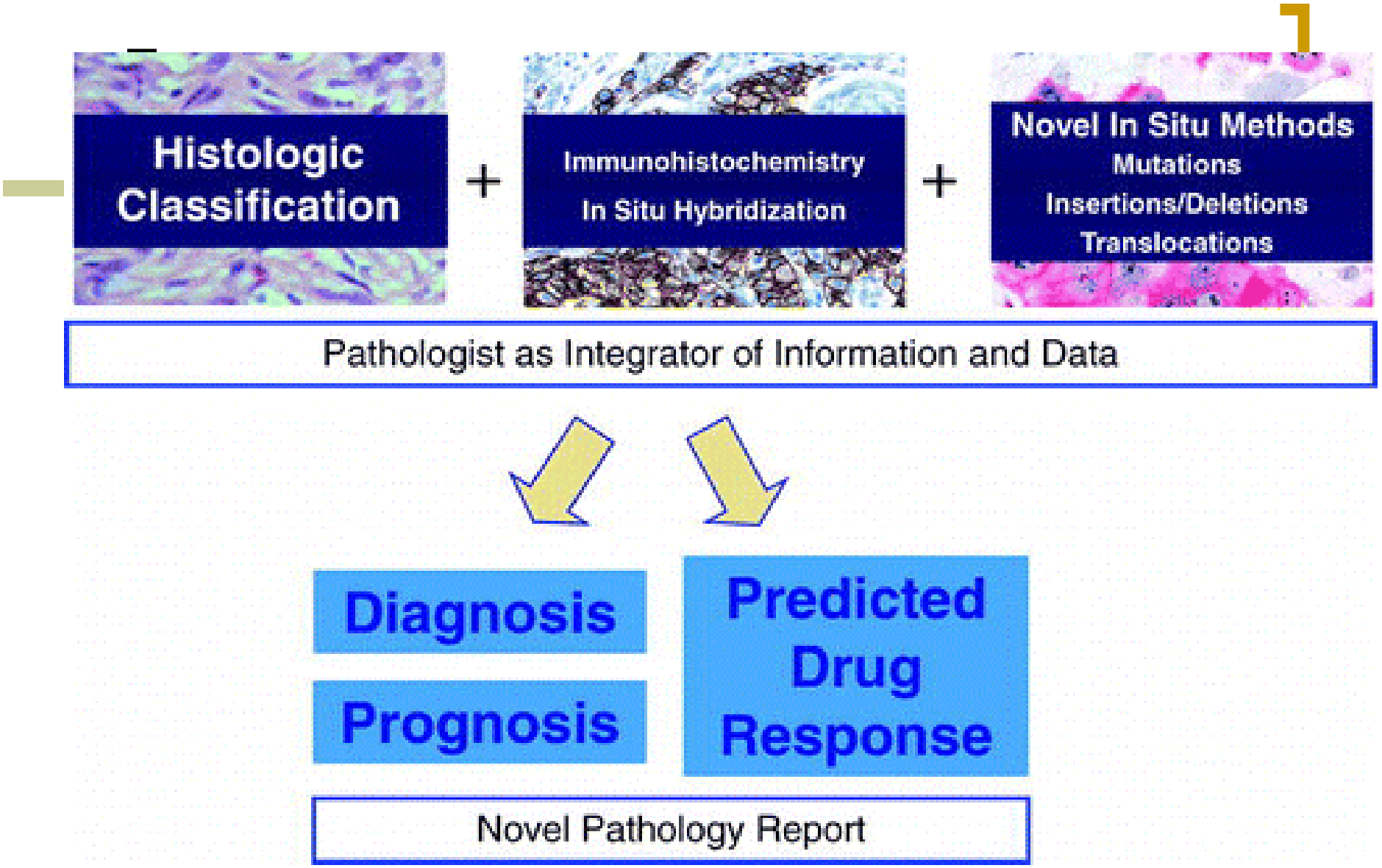


We are involved in the whole continuum of cancer care:

- Screening
- Diagnosis
- Prediction of therapeutic response
- Monitoring of cure
- Identification of risk factors

And now:

- Our role in targeted therapies.



Eric E Walk Arch Pathol Lab Med, 2009; 133:605-610

Pathologists are now beginning to be required to answer the following questions:

- How aggressive is the malignancy?
- Which specific genes are deregulated and drive the tumor?
- How many signaling pathways are involved?
- Which targeted therapy will be effective?
- If patient becomes resistant to initial therapy what pathways should be shut down?

QA/QC

- We are required to **apply quality issues** otherwise we will lose the battle.
- Quality assurance and quality management are crucial in the pre-analytical, analytical and in the post-analytical steps.
- **Central control** is paramount, along with accreditation issues.

Pathology / QA

- Accuracy
- Timeliness
- Completeness
- Availability
- The ability to change

Accuracy
Pre-analytical issues

- Specimen fixation
- Specimen delivery
- Specimen identification
- Adequacy of clinical history
- Accessioning errors.

Analytical issues

- **Intra-operative** assessment of SLNs, specimen margins and concordance with permanent sections.

- Final diagnosis and peer review error rate.

- Histology and grossing room monitors:
  -Paraffin block and slide quality.
  -Labeling errors (blocks, slides).

And some more…

- Immunohistochemistry:

  -Frequency of repeat slides.

  -External validation of relevant antibodies:

  ER, PR, Her2, Ki67.

- Molecular studies (**Her2-**FISH/

  CISH/SISH):

  -Concordance with IHC, statistics

  -External validation

Post analytical issues

- Transcription errors.
- Verification errors.
- Report delivery errors.
- Incomplete reports.
- Diagnostic finding correlation with ancillary studies (IHC, FISH).

Timeliness / Turn Around Time (TAT)

- Frozen sections.
- Cytology specimens.
- Core needle biopsies.
- Mammotome specimens.
- Lumpectomy / mastectomy specimens.
- Special studies (IHC, FISH).

Completeness of report

A full report should contain all the following:

- Demographic details.
- A comprehensive macroscopic description.
- Assignment of all paraffin blocks to specific locations.
- Diagnosis.
- Tumor grade.
- Tumor size.

Full report (cont.) :

- Margin status.
- Receptor status (IHC, FISH).
- SLN / cALND (protocol)
- Correlation with previous cytology, CNB, FS results.
- Concordance of diagnosis with ancillary results.
- Additional pathology in the breast tissue.

Cont….

Templates / Summary checklists–

- Make the writing of these very elaborate reports required today, easier to read by the clinicians.

- Make sure that all details are entered into the report.

Availability of the pathologist

- The multidisciplinary nature of the breast disease centers has taken the pathologist out of the laboratory into the clinical sphere where he belongs.
- The timely cross talk with the radiologists, surgeons and oncologists enables –
  - -To find out discrepancies as soon as possible.
  - -To learn and understand the different radiological, clinical and pathological setups

The ability to change is crucial…

- In this era of rapidly developing molecular testing and QA/QC requirements.
- In a multidisciplinary setup, in order to enable a smooth flow.
- This is not of course unique for pathology.

A few examples

- Her2 testing
- ER/PR testing
- Sentinel lymph node testing

Her2 testing

- As for all predictive markers, the testing must be of utmost accuracy.
- An example to issues that may influence pathological results.
- Multiple sources for variation, as listed above:

  -Pre-analytical

  -Analytical

  -Post-analytical

Factors underlying Her2-testing variation (Basel Herceptin team)

√ **Handling and pre-analytical preparation of tumor sample**

- - Time to slicing and fixation of the specimen
- - Thoroughness of tissue processing
- - Type of fixative and fixation duration
- - Storage of tissue blocks and sections
- - Pretreatment procedures, e.g. antigen retrieval, protease pretreatment

√ Her2-testing methodology

- - Her2-testing protocol (is it standardized/validated?)
- - For IHC, antibody/kit used
- - For ISH techniques, probe/kit used
- - Test reagents and storage
- - Controls
- - Assay conditions, e.g. temperature, duration of incubation steps
- - Use or not of automation platform and/or image-analysis system

√ **Interpretation and reporting of results**

- - Interpretation of controls
- - Scoring system
- - Reporting elements

Optimal Testing

- **Accurate and reproducible** test, based on GLP.
- **Concordance** testing – to be performed by lab before routinely issuing HER2 results (>95% agreement or <5% disagreement).
- Equivocal tests – **confirmatory** testing.
- **Accuracy** testing – comparing to gold standard, however there is **no** gold standard at present.

- Troubleshooting
- Minimal recommended case load in local lab.
- The role of the reference lab.
- Responsibility of head of service.
- External QC.

A solution - Guidelines, for…

- Improved outcomes.
- Improved medical practice.
- Minimizing inappropriate practice variation.
- Decision support for practitioners.
- Reference points for medical education.

Continued…

- Self evaluation criteria.
- Enable external quality review.
- Reimbursement decisions.
- Identification of areas where further research is needed.

However Guidelines…

- Cannot account for individual variation among patients.
- Are not to supplant physician’s judgment .
- Are not inclusive of all proper methodology.
- Are not exclusive of other treatments that may obtain same results.

Continued…

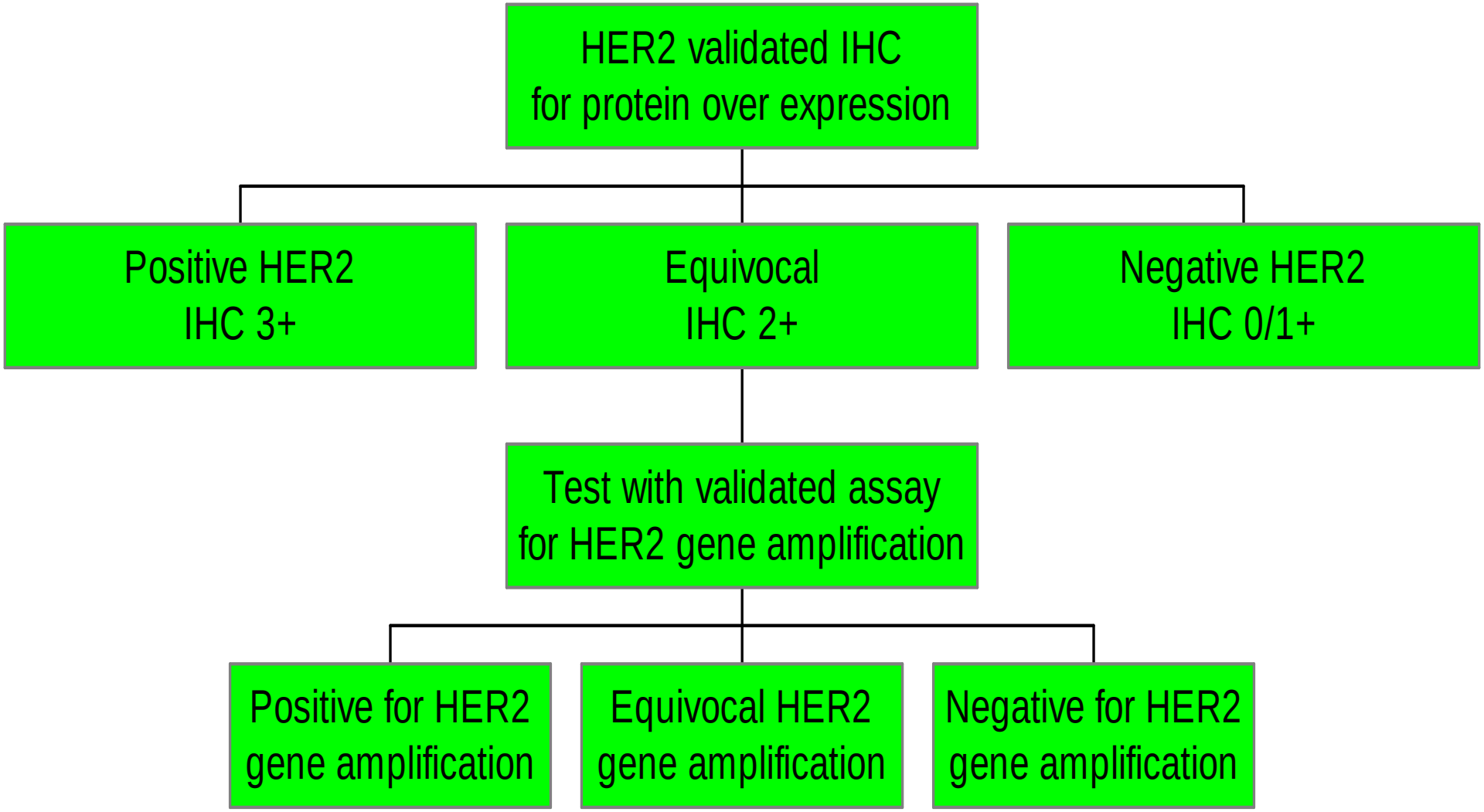
Therefore ASCO/CAP consider

adherence to these guidelines to be **voluntary**

with the ultimate determination regarding their application to be made by the physician in light of each patient's circumstances.

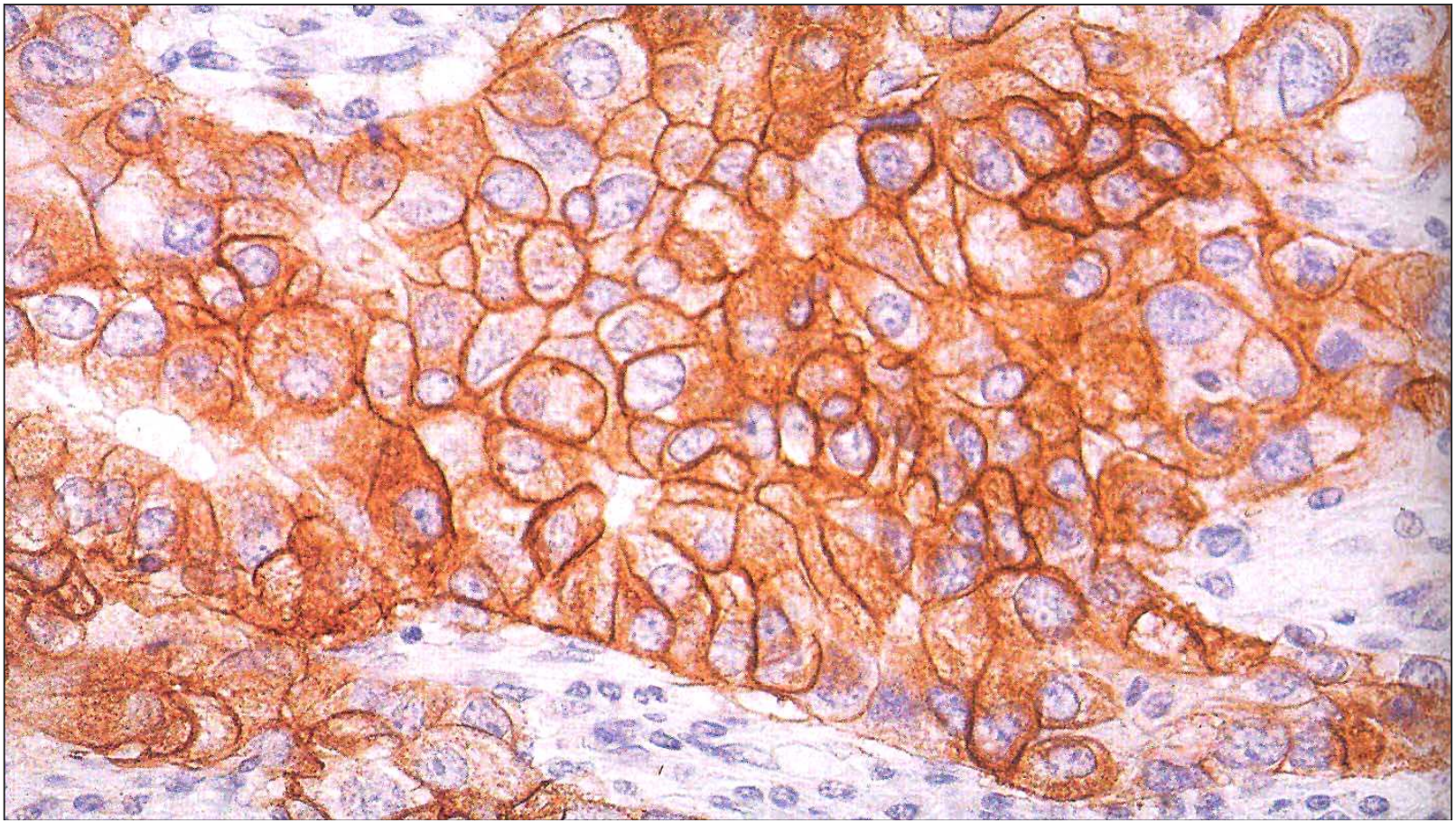
Pre-analytical	Analytical	Post-analytical
Time to fixation	Assay validation	Interpretation
Method of tissue processing	Equipment calibration	Image analysis
Time of fixation	Standard Laboratory Procedure	Reporting
Method of fixation	Staff training assess.	QA procedures:
Specimen delivery	Antigen retrieval	-lab accreditation
Specimen identification	Test reagents	-Proficiency tests
Accession errors	Standard controls	-pathologists…
Clinic.Hx adequacy	Automation	

Her2 Testing Algorithm

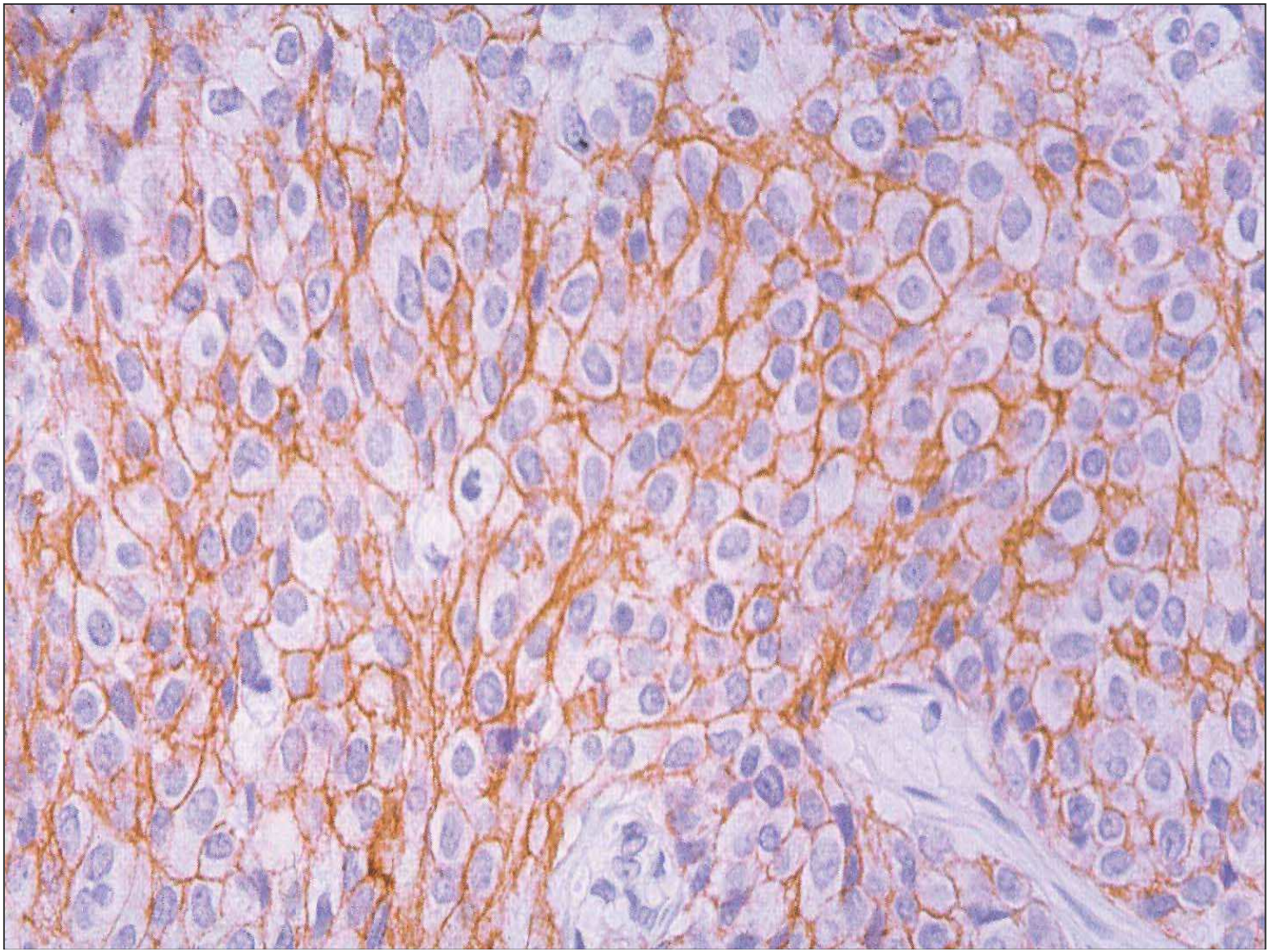


Immunohistochemistry (IHC) – Her2

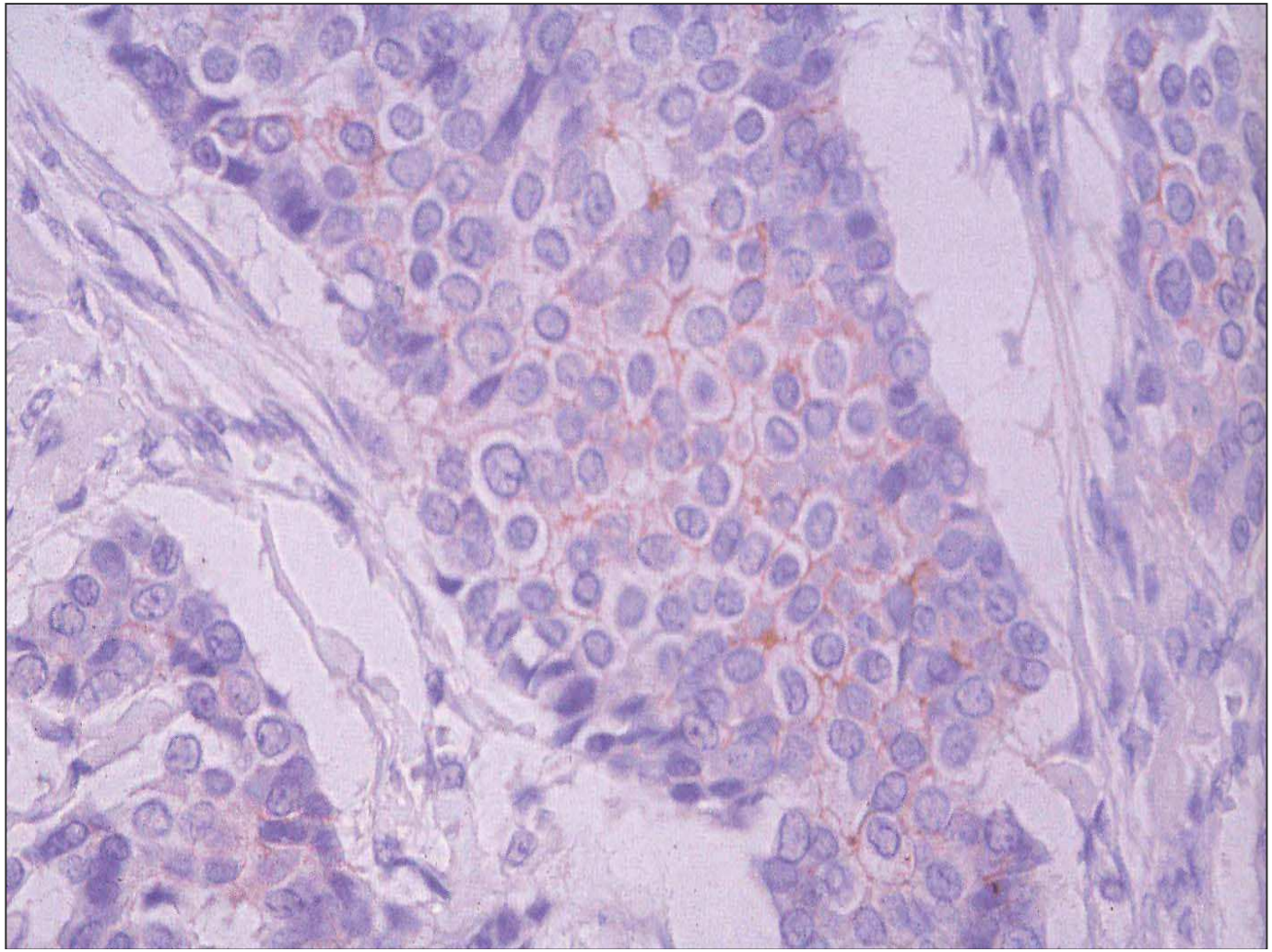
3+ Uniform, intense membrane staining of >30% of invasive tumor cells

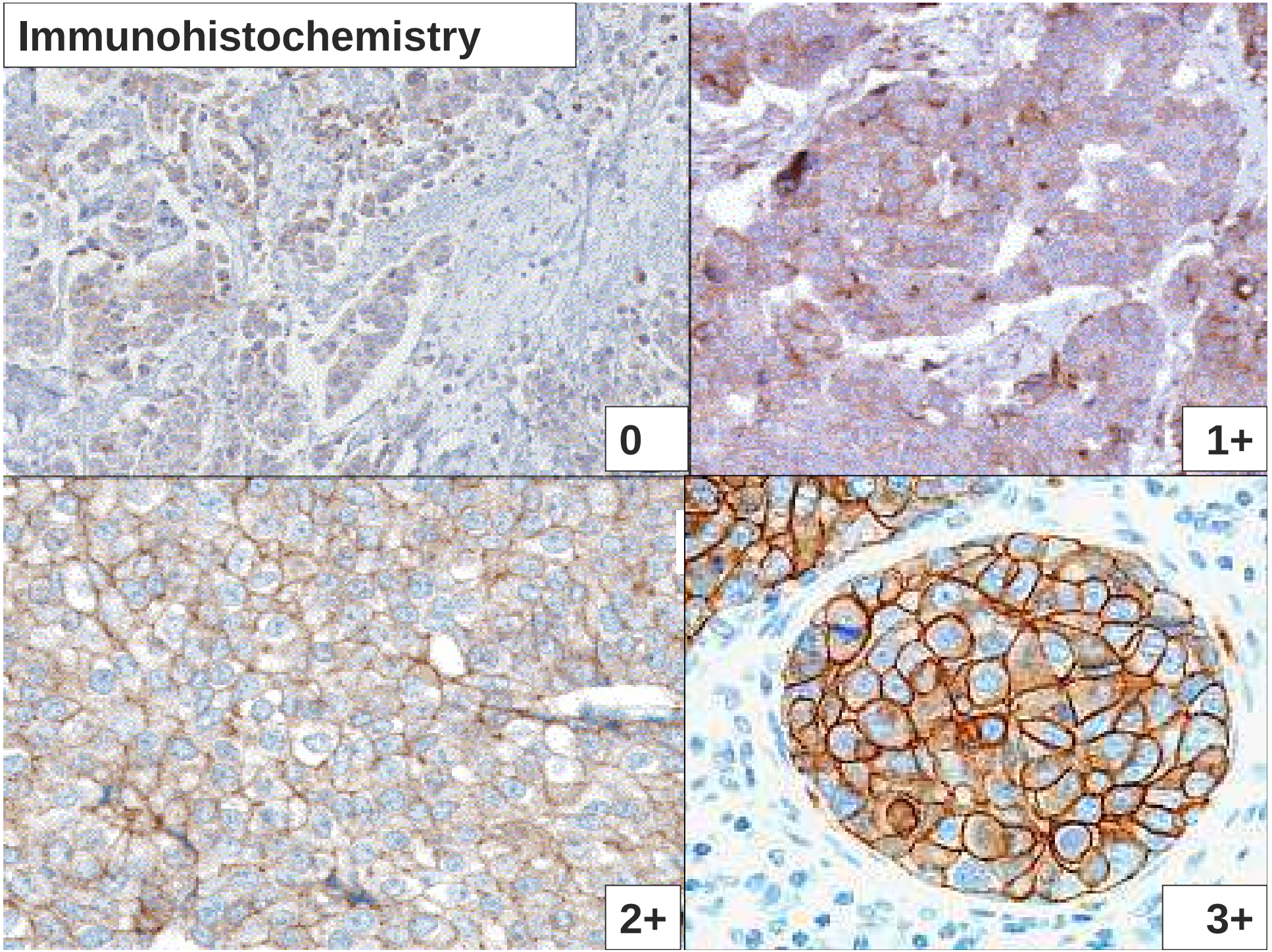


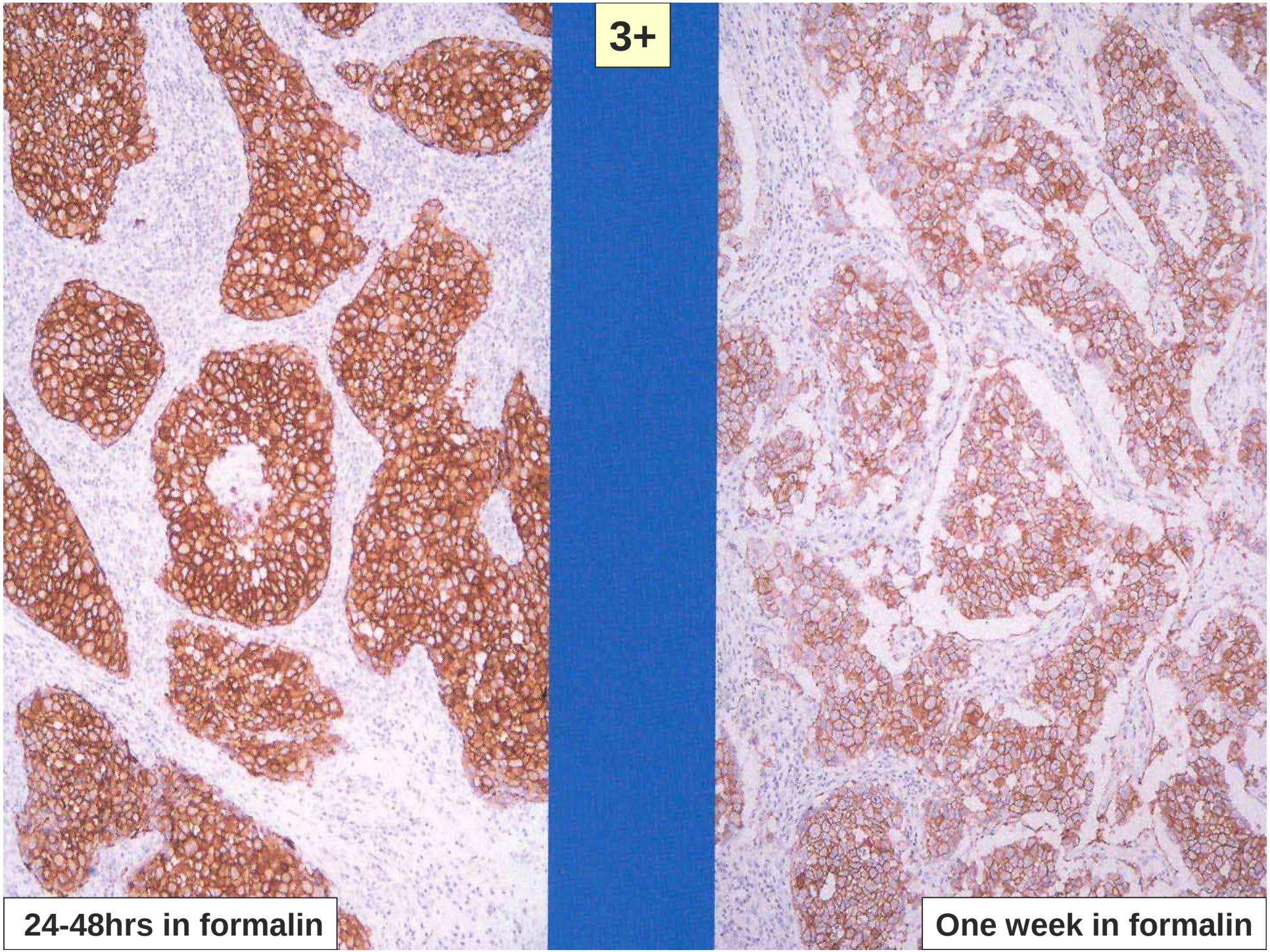
2+ Complete but weak membranous staining in at least 10% of tumor cells

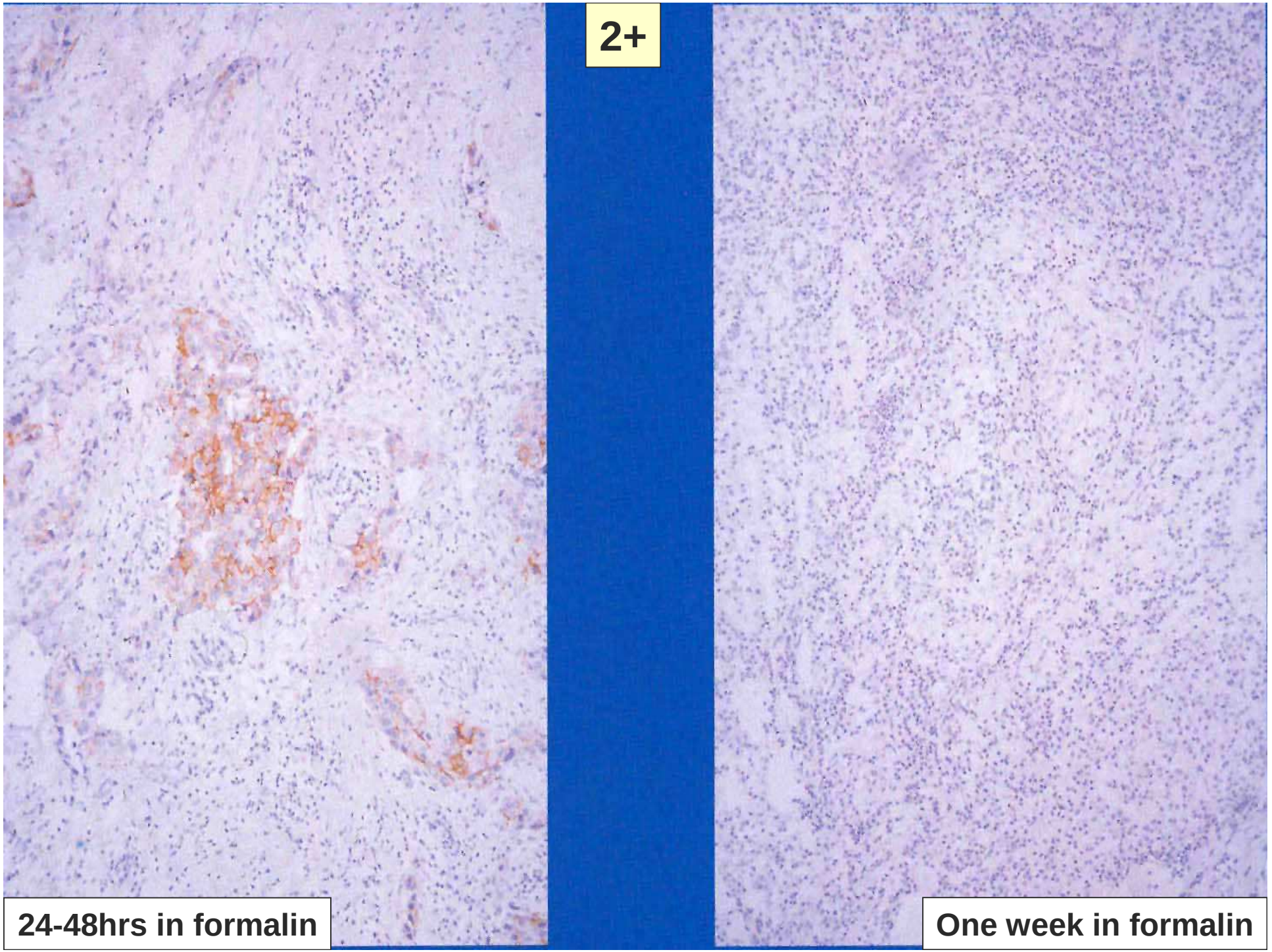


0 /1+ No or weak incomplete membrane staining in any proportion of cells.
(Upper limit of 5% false-negatives should be avoided and brought to as close to 0 as possible).




Immunohistochemistry
0
1+
2+
3+


3+
24-48hrs in formalin
One week in formalin


2+
24-48hrs in formalin
One week in formalin

QA programs

Canada

- x2 a year each lab sends 10% Her2 (2+) and 10% Her2(-ve) cases.
- A 90% concordance level is required.
- Frequent teaching sessions and workshops.

NordiQC

- Multi-block slides are distributed.
- Results assessed.

UKNEQAS

- Slides with breast cancer cell lines, sent to pathology labs.
- Pathology labs stain slides.
- Slides assessed centrally.
- Consistently poor performance → The lab will be removed from IHC/ISH UK NEQAS register and loss of accreditation for this test.

USCAP

- TMA slides stained locally and interpretation results evaluated.
- IHC – 40 challenges x2 a year.
- ISH – 10 challenges x2 a year.
- If lab does not reach concordance level – the lab may be suspended until performance corrected.

AFAQAP (France)

- Slides distributed for Her2 testing in pathology labs.
- Stained slides are returned for assessment.

Laboratory accreditation

- Formal recognition that a lab is competent to carry out a specific test.
- Minimal standards are required for the following:
  - External QA
  - Internal QC
  - SOPs
  - Personnel education and training
- Accreditation programs exist in the US and the UK.
- Ring studies – Inter-lab interpretation consensus.

ER/PR Testing

- In Canada a very large-scale investigation into ER/PR testing has discovered a very problematic issue:
  - ~2000 ER(-ve) patients were retested in another lab and 40% were found to be ER(+).
- UK NEQAS revealed significant errors in ER/PR IHC testing.
- ASCO/CAP, 2010, Guideline recommendations for ER/PR IHC testing.

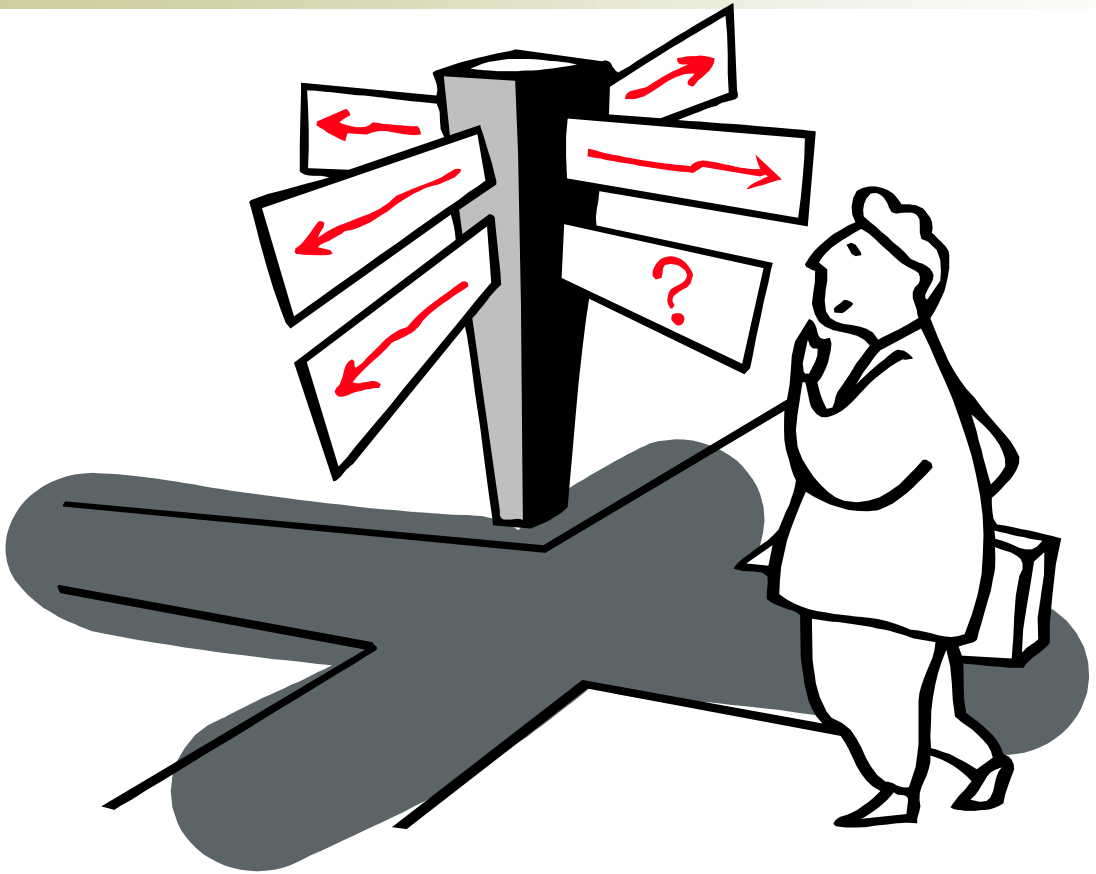
Budget issues

- This developing field in pathology has to be recognized centrally, because we are shifting rapidly to expensive testing.
- This is not a new issue, however, as more and more drugs are being developed and more genes are recognized to play a role in specific diseases, we will have to deal with more expensive tests and **programmed** funding is required.

Other issues…

- Morphology and the rapidly developing protein and molecular testing together with numerous prognostic and predictive issues are required to be included in the pathology **reports/templates.**
- Pathology **training** programs.
- Pathologists in industry

Pathology at a crossroads

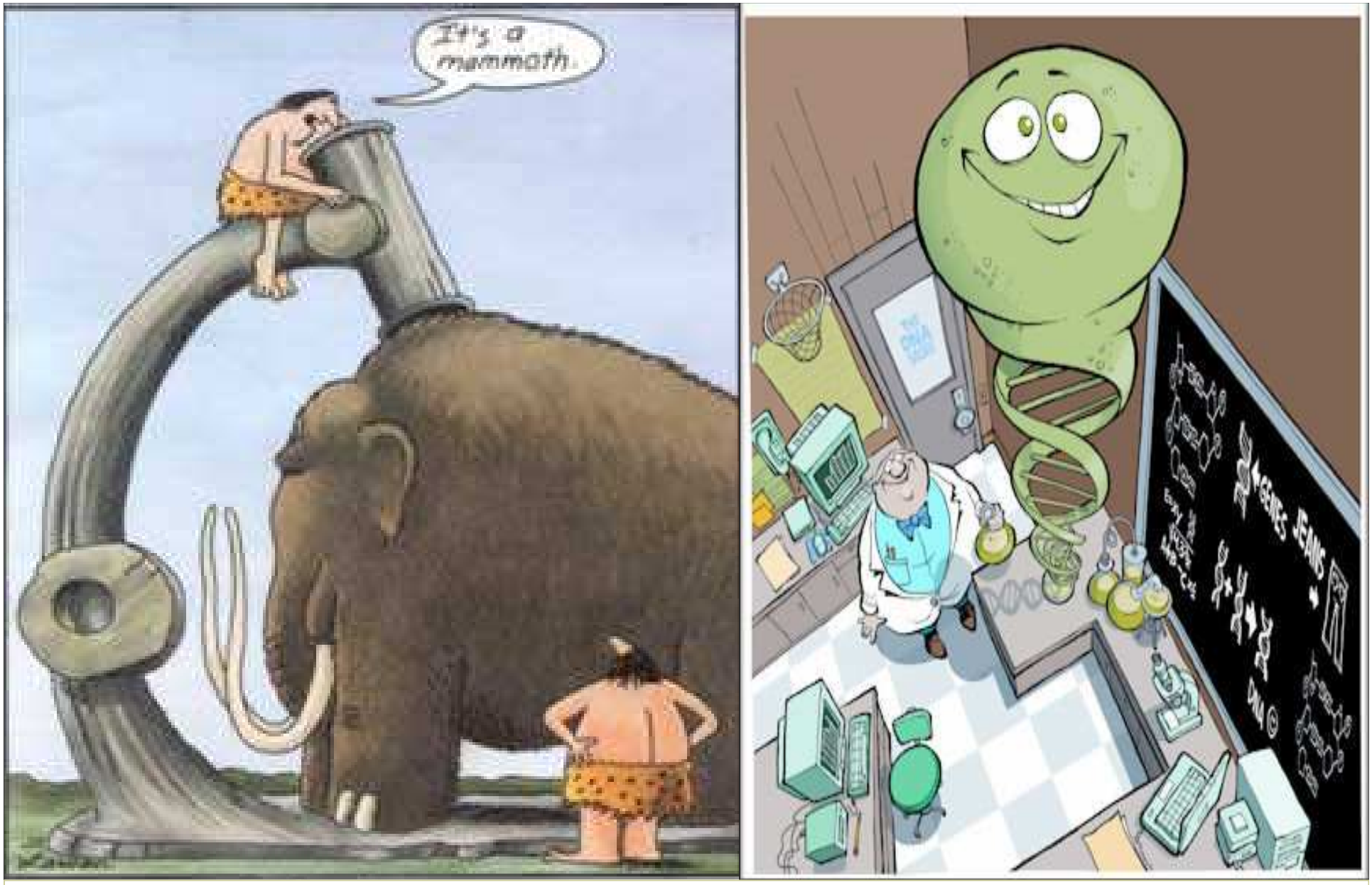


An important barrier is our own: We the pathologists must realize the change that is occurring, participate in it and keep all tissue based tests in our field.

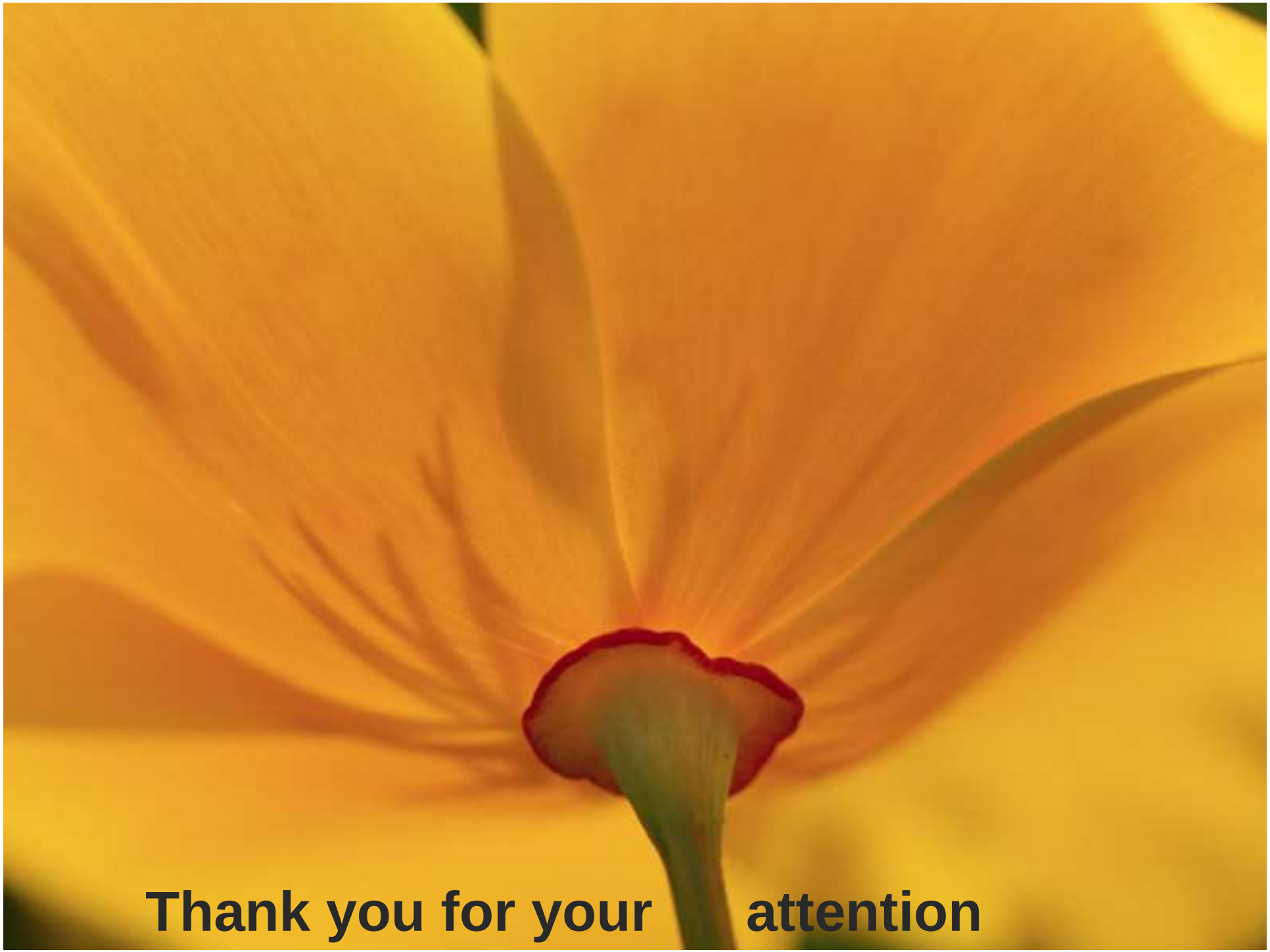
In conclusion

For pathology to remain relevant in a breast disease center setup :

- It has to be able to provide personalized-medicine information.
- It has to relate to diagnosis, prognosis, response prediction.
- It has to help create new tools for tumor characterization.
- It has to adopt high quality standards.
- It has to adjust budgeting.



Pathology/Early microscope versus **Molecular biology**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