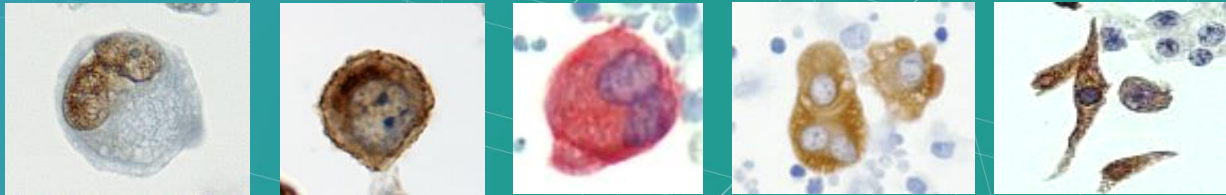

Immunocytochemistry – overview, considerations and applications

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UNIVERSITY OF LJUBLJANA ♦ FACULTY OF MEDICINE

Sources

EFCS surveys

- Immunocytochemistry

- 245 participants; 94% from 26 European countries, 6% from 5 non-European countries
- Cancer Cytopathol. 2020;128(10):757-766. doi:10.1002/cncy.22311

- Cell blocks

- 402 participants; 97% from 27 European countries, 3% from 10 non-European countries

UK NEQAS ICC results

Our studies and experiences

- Preservation of biomarkers immunoreactivity on cytopins protected with polyethylene glycol. Cytopathology. 2021; 32: 84– 91.
- Time-related changes in cell morphology and biomarker immunoreactivity for cells stored in a buffer-based cell medium. Cytopathology. 2021;32(4):513-518.
- Immunocytochemistry practices in European cytopathology laboratories - review of European Federation of Cytology Societies (EFCS) online survey results with best practice recommendations, Cancer cytopathology 128 (10): 757-766, 2020.
- Cell count-based triaging of cytology samples for cell block preparation, Cytopathology.2016; 28(3): 216-220.
- Optimization and validation of immunocytochemical detection of oestrogen receptors on cytopins prepared from fine needle aspiration (FNA) samples of breast cancer, Cytopathology. 2015;26(2): 88-98.
- External quality control for immunocytochemistry on cytology samples : a review of UK NEQAS ICC (cytology module) results, Cytopathology.2011; 22(4): 230-237.
- Haemorrhagic cytology samples: how to get the best diagnostic results, Cytopathology.2007; 18(3):175-179.
- MIB-1 immunostaining on cytological samples: a protocol without antigen retrieval, Cytopathology.2004; 15(3):154-159.

Immunocytochemistry (ICC) = IHC on cytology samples

Cytology

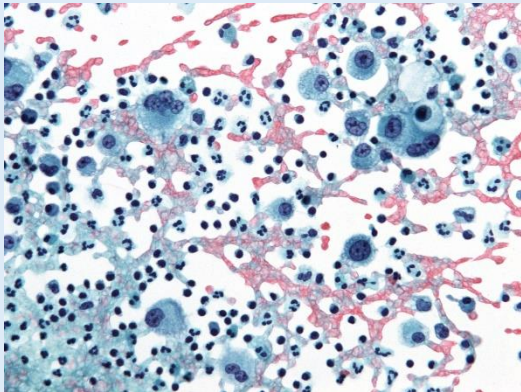
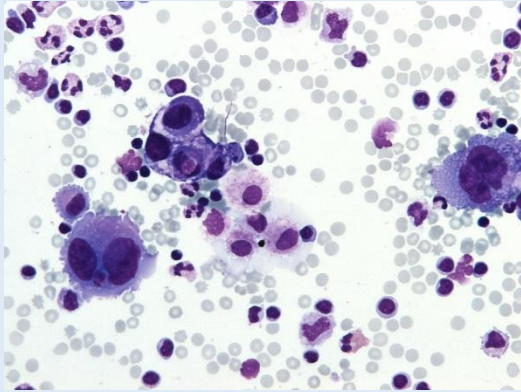
- Minimally invasive diagnostic method
- First line, sometimes ONLY available
- US-FNA, EUS-FNA

ICC

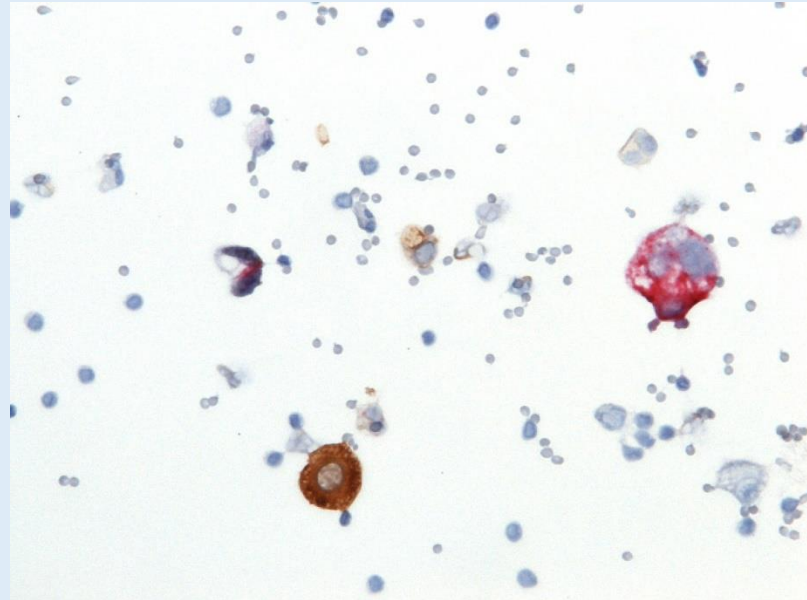
- Tumor typization
- Metastasis origin
- Prognostic/predictive

Value of ICC in a modern cytopathology- effusions

Pleural effusion, M, 80 yrs, ca pancreas

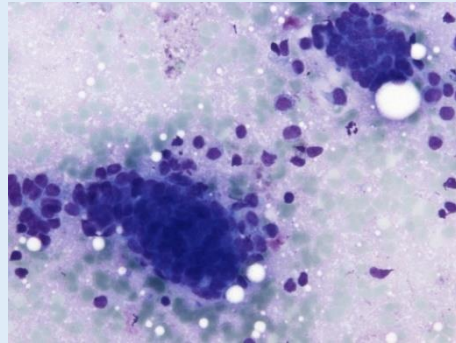


Double ICC – Calretinin/MOC31

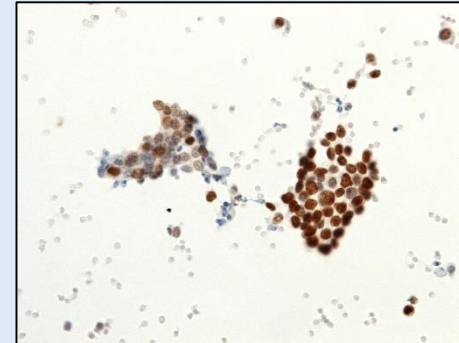
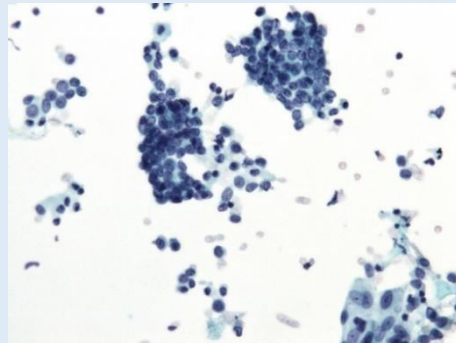
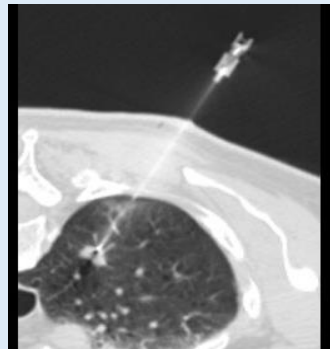


Value of ICC in a modern cytopathology - breast cancer- hormone receptor status

F, 87 yrs, tumour in right breast 4 x 3,5 cm



ER



PR

Biomarkers – lung cytology

Thursday afternoon

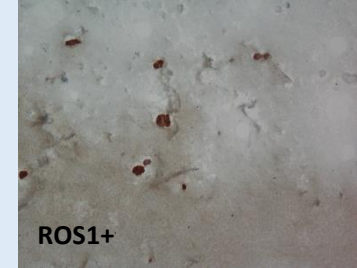
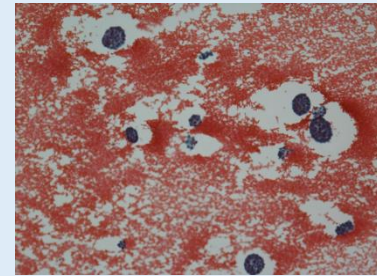
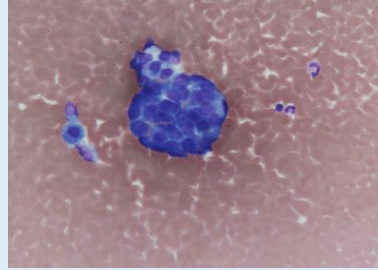
Pericardial effusion, M, 38 yrs
on intensive care

Smoker, cough, fatigue, weight
loss

Infiltrates in lung

Cytospins + cell block

Cytospins



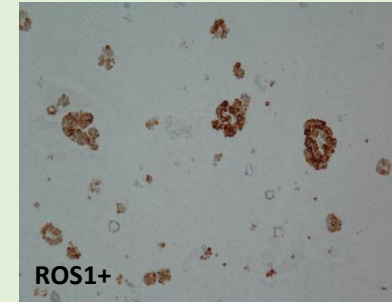
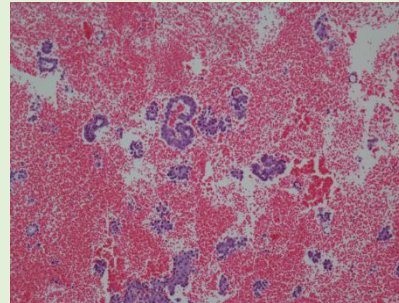
Immediate ROS TK1 treatment

Monday

IHC+FISH ROS1 positive

After 4 years ROS1 + metastasis

Cell block



Immunohistochemistry (IHC)

=

Immunocytochemistry (ICC)

- Principles
- Basic steps
- Antibodies
- Reagents
- Platforms
- QA/QC measures

Immunohistochemistry (IHC)

≠

Immunocytochemistry (ICC)

Pre-analytical

- Sample management and processing
- Fixation

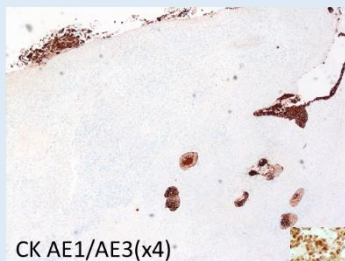
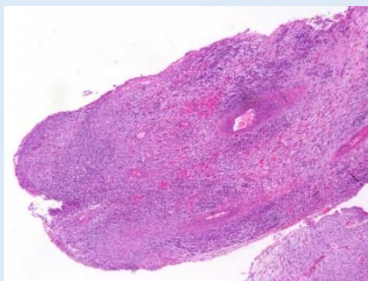
Analytical

- Pretreatment
- Dilutions
- Detection kits

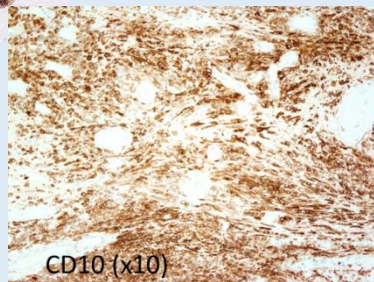
QA/QC

- Control slides
- Optimization
- Validation

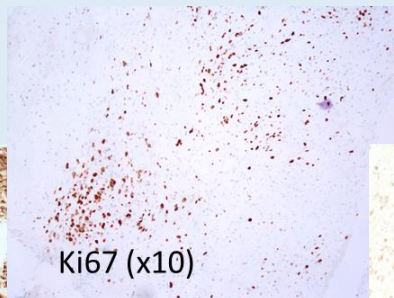
Histology – IHC workflow



CK AE1/AE3(x4)



CD10 (x10)



Ki67 (x10)



P53 (x20)

Cytology –ICC workflow

On site immediately

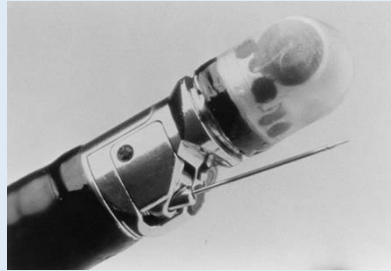
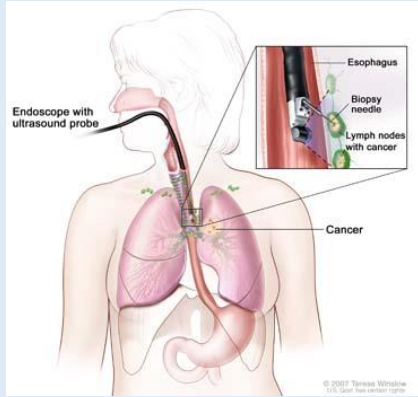
Diagnostic smears

Smear for **R**apid **O**n **S**ite **E**valuation (ROSE)
sample adequacy ? ancillary test ?



Sample for ICC, special stain, flow
cytometry, FISH, ISH, molecular test ?

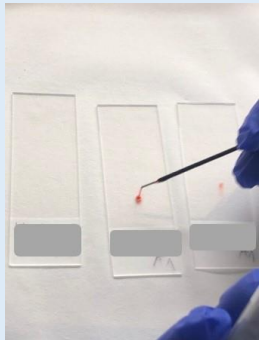
Endoscopic ultrasound guided fine-needle biopsy (EUS-FNBs)



Immediate on site
evaluation of sample
adequacy and
cellularity

Rapid On Site Evaluation - **ROSE**

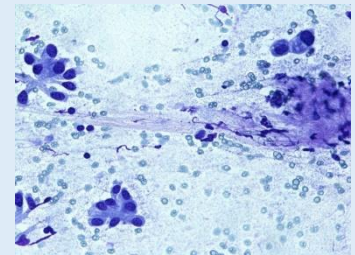
Smears for morphology



Smear for ROSE



Cell medium



Laboratory workflow



Cytomorphology



Cell pellet stored at -70°C for potential molecular testing

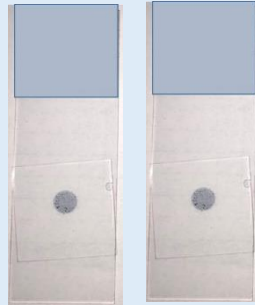
SY-CB



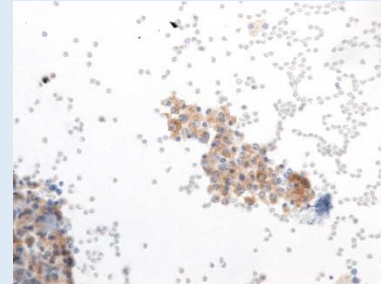
KROM-CB



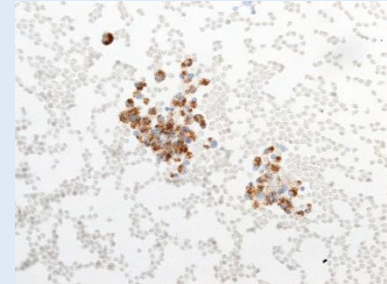
ROSE



SY- cytopsin



KROM- cytopsin



Cytology – **ICC workflow**

- Low and unknown sample volume/cellularity
- Sample adequacy
- Immediate decision for ancillary methods

Cytology sample processing – **slide preparation** options

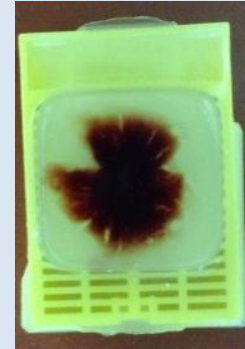
- Cell blocks
- Direct smears
- Cytospins
- Liquid based cytology – LBC

Cell blocks

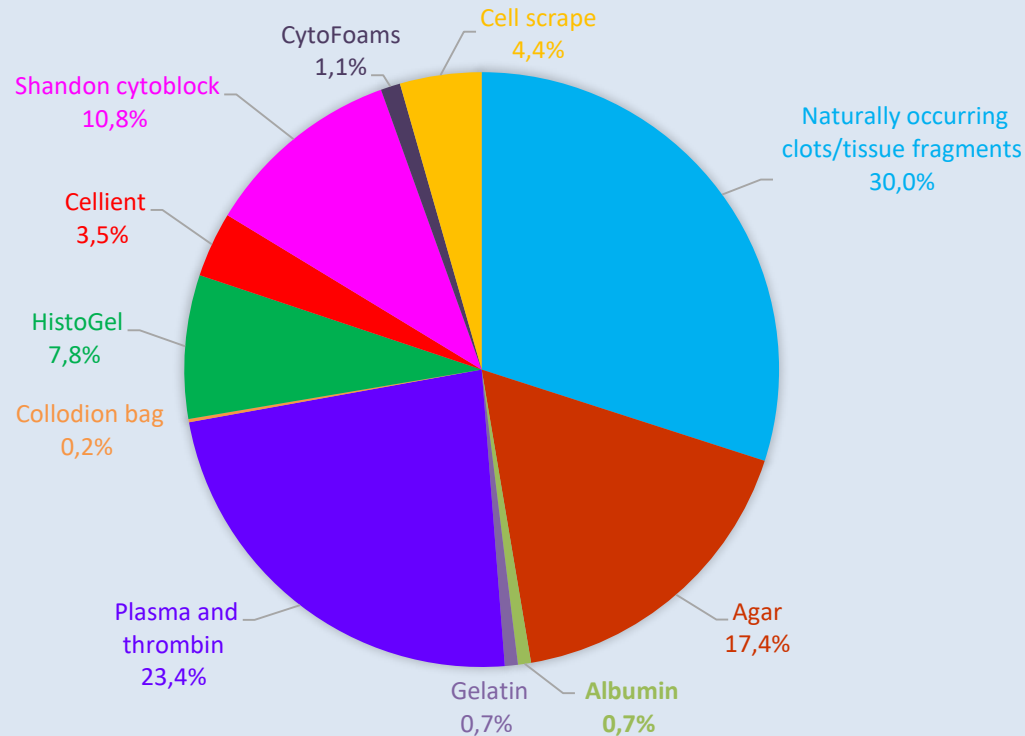
FFPE cell blocks $\approx$ FFPE tissue samples

Advantages

- easy storage
- multiple sections
- same protocols as for FFPE
- same QC/QA
- no additional validation studies



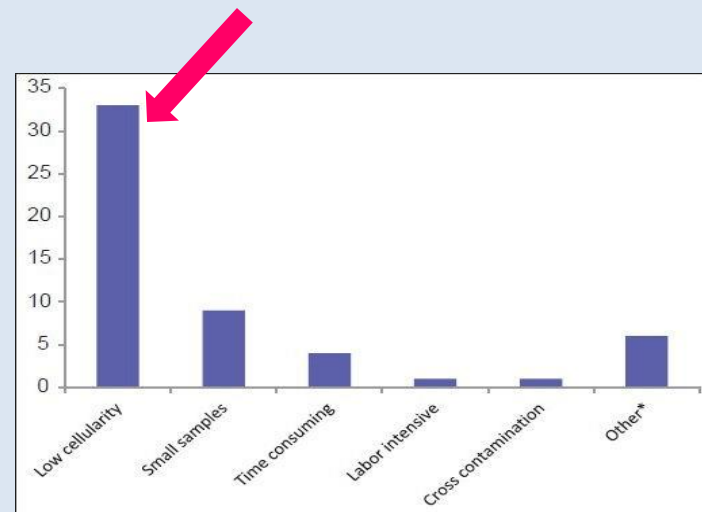
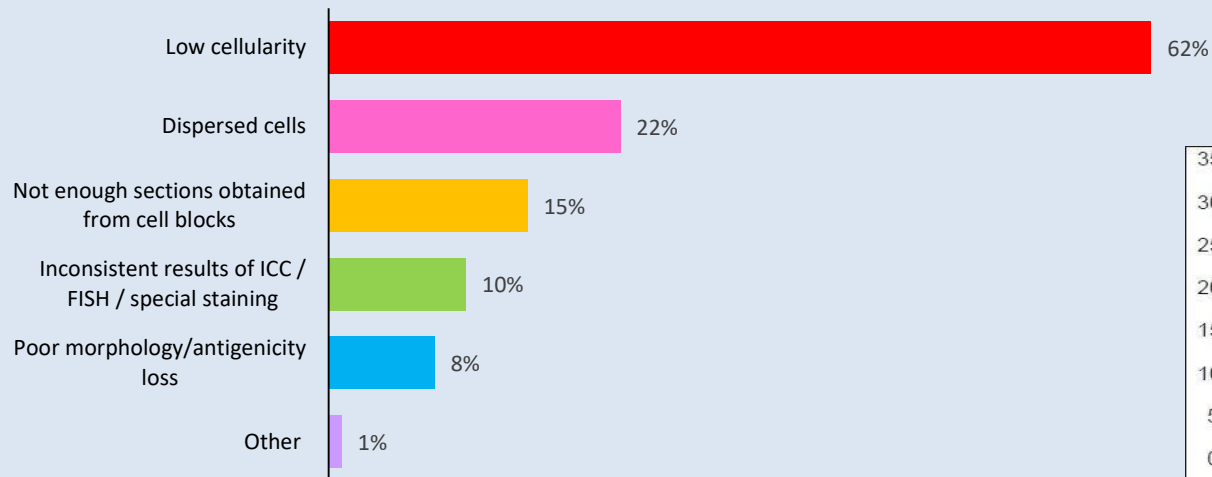
Cell block preparation methods – EFCS survey



Cell blocks - disadvantages

- no standardized protocol
 - medium for sample collection (fixative, PBS, commercial solutions, RPMI, other)
 - fixation (formalin and non- formalin based)
 - cell pellet preparation (agar, HistoGel, plasma thrombin, Cellient, ...)
- **not suitable for low cellular samples**
- time consuming (↑ TAT)
- ↑ price
- sample triaging

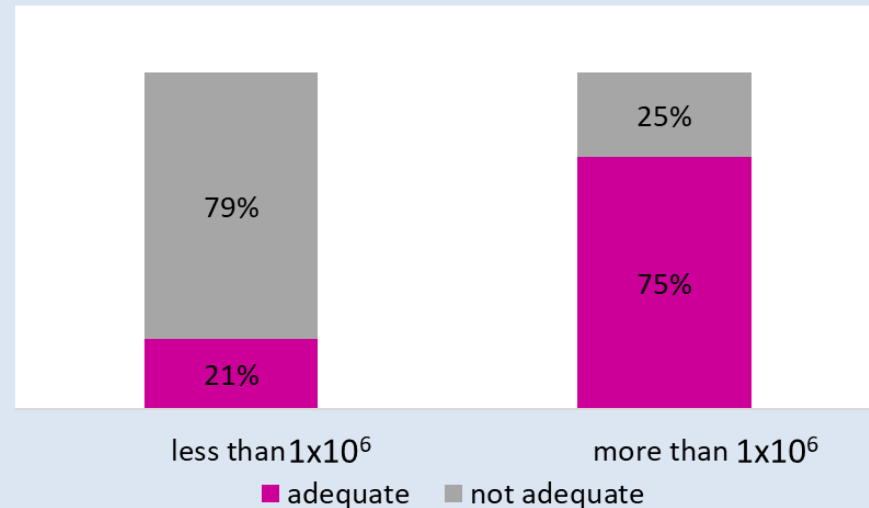
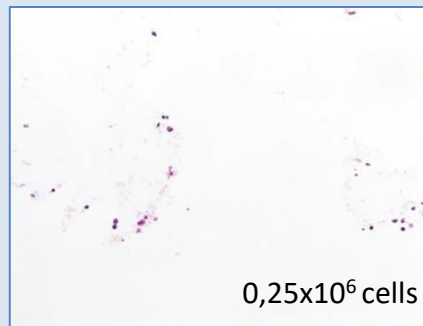
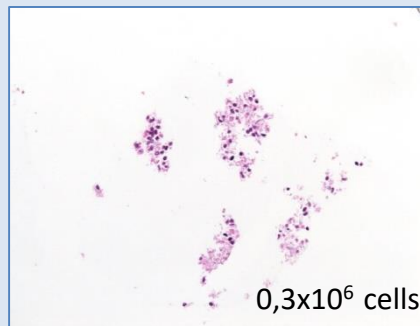
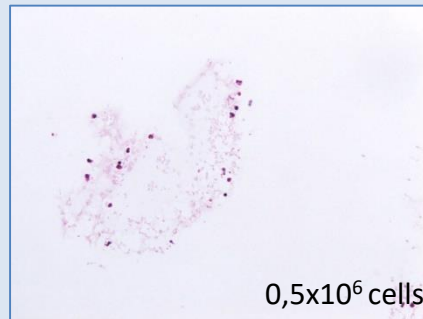
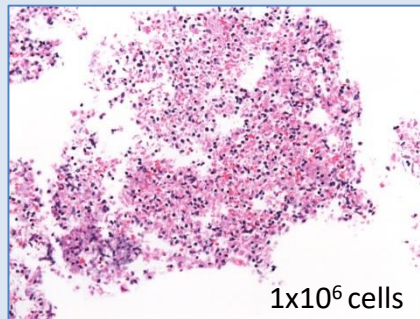
Issues with CB



Crapanzano, J. P., Heymann, J. J., Monaco, S., Nassar, A., & Saqi, A. (2014). The state of cell block variation and satisfaction in the era of molecular diagnostics and personalized medicine. *CytoJournal*, 11, 7. <https://doi.org/10.4103/1742-6413.129187>

CB cellularity – number of cells embedded

CB from aliquotes of the same sample with different cellularity



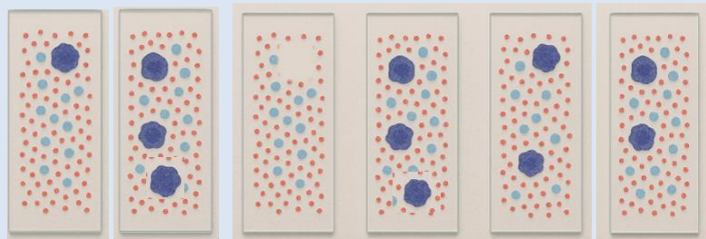
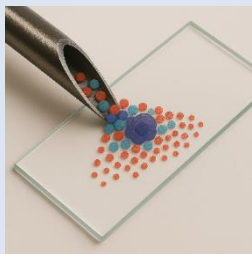
Alternatives to cell blocks

- Establishing a protocol for ICC staining and CISH of Giemsa and Diff-Quick **prestained cytological smears** (E. Beraki, TK Olsen, T Sauer, CytoJournal **2012**)
- The application of ICC to **direct smears** of metastatic Merkel cell carcinoma (SM Knoepp et al. Diagn Cytopathol **2013**)
- ER, PR, and Her2 immunocytochemistry on cell-transferred **cytologic smears** of primary and metastatic breast carcinomas: a comparison study with formalin-fixed cell blocks and surgical biopsies (Ferguson J et al. Diagn Cytopathol. **2013** Jul;41(7):575-81. doi: 10.1002/dc.22897. Epub 2012 Jul 16.

Smears

Advantages:

- always available
- quick, simple, inexpensive

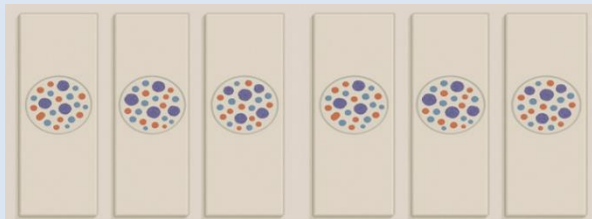


Disadvantages:

- sample triaging: which case/ how many smears
- uneven and uncontrolled distribution of the cells
- background ICC staining
- **unstandardized:**
 - unstained, Papanicolaou stained, MGG, Diff-Quick
 - fixation: drying before or after, acetone, ethanol based, formalin based, combination of fixatives, one step, multi steps
 - storage: freezer, refrigerator, RT, dried, in a fixative, PEG

Cytospins

slides prepared by cytocentrifuge from cell suspension



Advantages

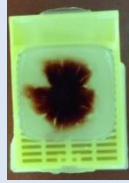
- **multiple slides**
- monolayer, controlled distribution of the cells
- short or long term storage of cell suspension/slides
- postponed decision for ancillary tests

Disadvantages

- cytocentrifuge
- non standardized procedure
- knowledge, experience, cooperation

Suitable for low cellular samples

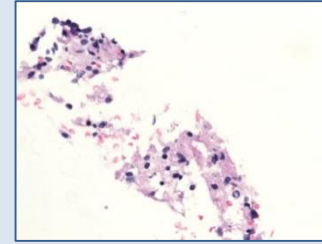
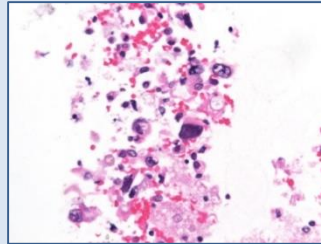
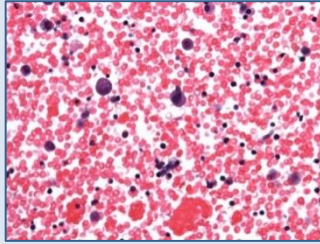
20×10^6 cells



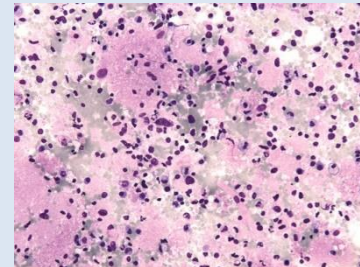
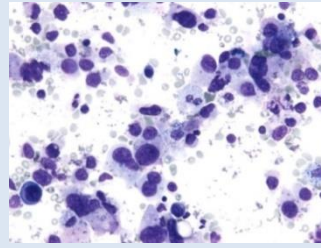
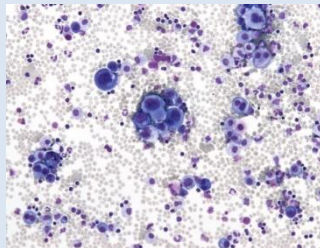
1.2×10^6 cells



0.1×10^6 cells



corresponding cytopspins

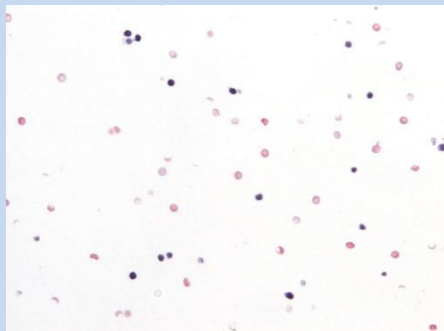


Cytospins

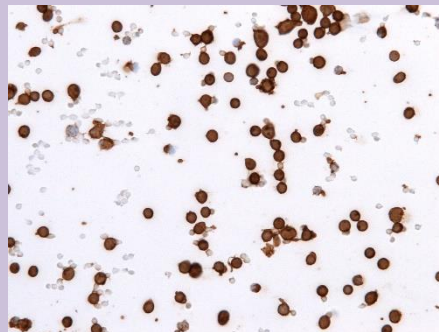
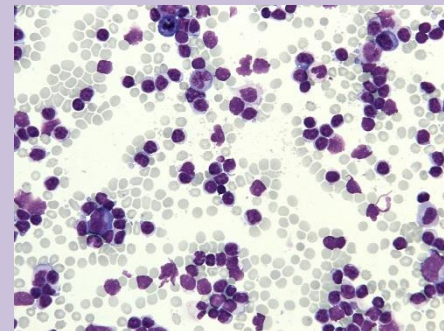
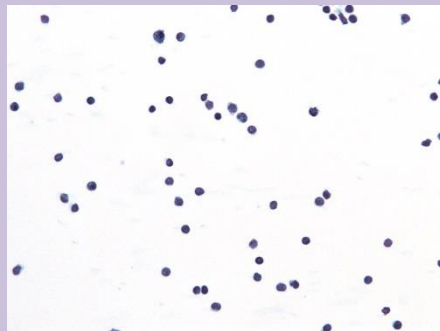
Knowledge, experience, cooperation

Stokes B.O. Principles of cytocentrifugation. *Lab. Med.* 2004;35:434–437.

Cell block



Cytospins



← CD45 →

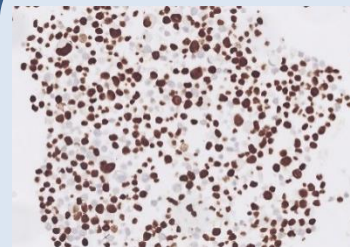
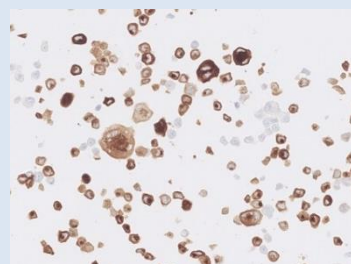
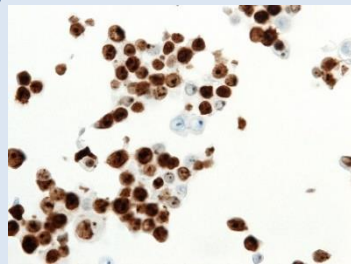
ER

Ki67

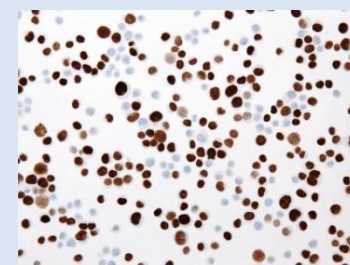
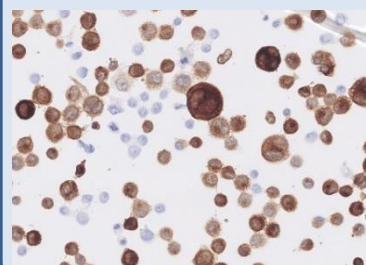
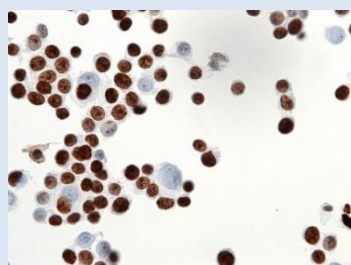
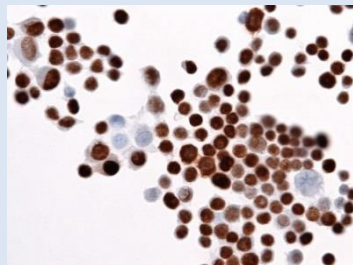
MelanA

p40

CB



Cytospin



Liquid based cytology (LBC)

- sample suspended in commercial transport medium
- automated slide preparation (ThinPrep, SurePath, CellPrep....)
 - membrane filtration
 - gradient centrifugation



LBC

Advantages

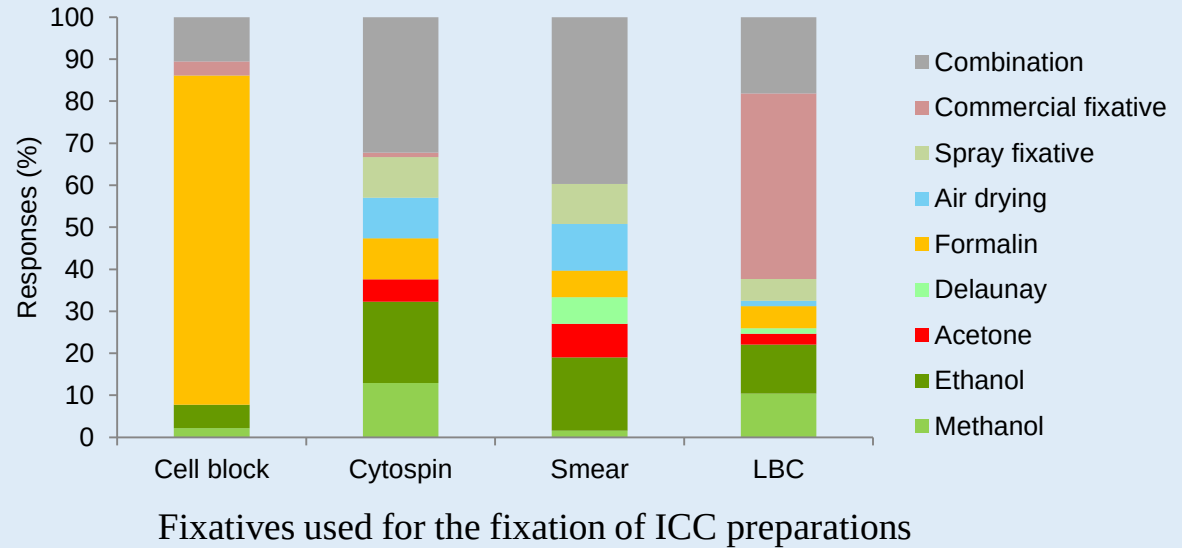
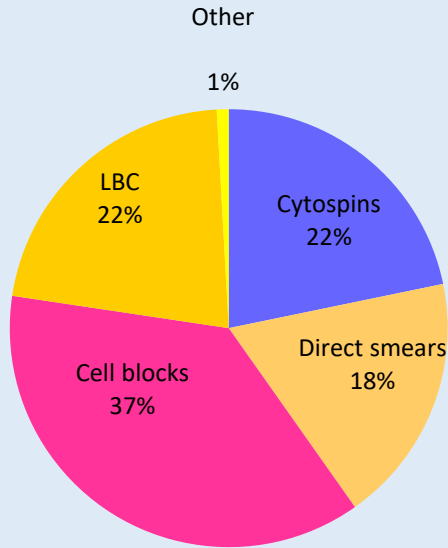
- easy storage of samples
- postpone decision
- monolayer distribution of cells
- multiple slides

Disadvantages

- expensive equipment
- ↑ cost
- Prefixed cells - clumping



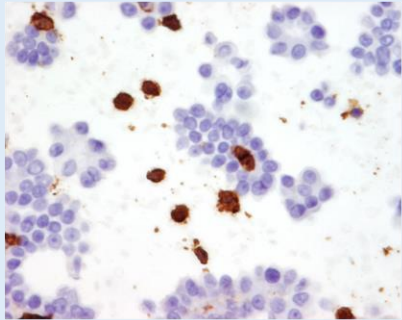
Slides used for ICC – European survey



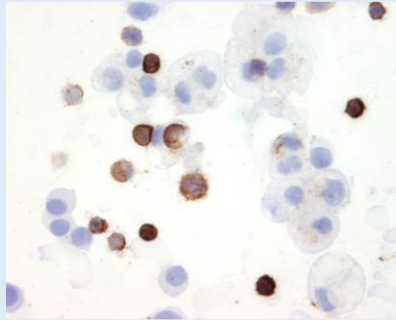
Srebotnik Kirbiš I, Rodrigues Roque R, Bongiovanni M, Strojan Fležar M, Cochand-Priollet B. Immunocytochemistry practices in European cytopathology laboratories-Review of European Federation of Cytology Societies (EFCS) online survey results with best practice recommendations. Cancer Cytopathol. 2020;128(10):757-766.

Good ICC quality can be achieved on a differently prepared slides

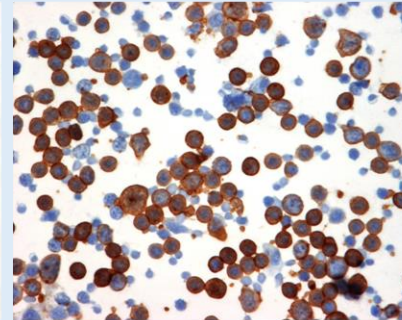
CD 45 (DAKO M701)



Cell block, FFPE



Smear, ethanol



Cytospin, methanol

Kirbis IS, Maxwell P, Flezar MS, Miller K and Ibrahim M. External quality control for immunocytochemistry on cytology samples: a review of UK NEQAS ICC (cytology module) results. Cytopathology 2011, 22, 230–237.

ICC reality

- Processing of cytology samples for ICC is not standardized
- Great variability in all aspects of ICC on cytology samples
- Good ICC quality can be achieved on a differently prepared slides
- Reliability of ICC (correct, accurate, repeatable)?

Quality assurance/quality control (QA/QC)

Why?

- Reliable ICC results (correct, accurate, repeatable)
- Accreditation

How?

- Control slides
- ICC optimization and validation
- External quality control (EQA)

- Institute CLS. Quality assurance for design control and implementation of immunohistochemistry assays: approved guideline, second edition. CLSI Document I/LA28-A2: Clinical and Laboratory Standards Institute; 2011.
- Hardy LB, Fitzgibbons PL, Goldsmith JD, Eisen RN, Beasley MB, Souers RJ, et al. Immunohistochemistry validation procedures and practices: a College of American Pathologists survey of 727 laboratories. Arch Pathol Lab Med. 2013;137(1):19-25.
- Torlakovic EE, Riddell R, Banerjee D, El-Zimaity H, Pilavdzic D, et al. Canadian Association of Pathologists-Association canadienne des pathologistes National Standards Committee/Immunohistochemistry: best practice recommendations for standardization of immunohistochemistry tests. Am J Clin Pathol. 2010;133(3):354-65.

Control slides

Positive control slides

- Sample with known expression of antigen
- Prepared as patients sample

Check:

- staining procedure
- antibody reactivity

Negative control slides

- Additional slide from diagnostic sample
- Replacing primary antibody with diluent buffer

Check:

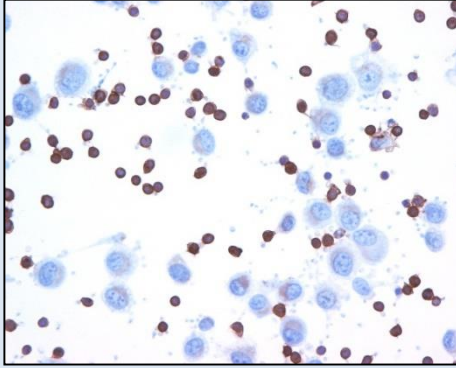
- non-specific staining

Control should be prepared the same as test sample*

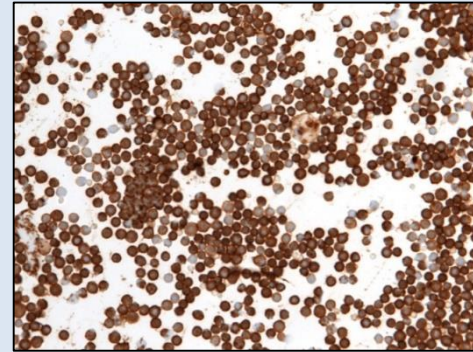
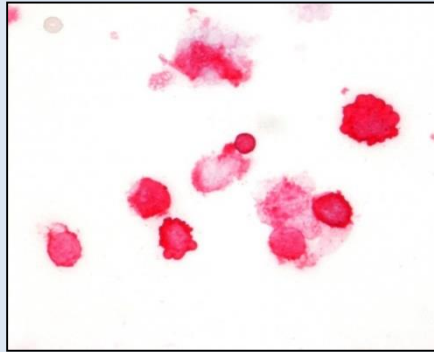
Sample	Control
FFPE tissue	FFPE tissue
Cell blocks -Histogel	Cell blocks -Histogel
Cell blocks - Shandon	Cell blocks - Shandon
Cell block - other	Cell block - other
Cytospins - methanol	Cytospins - methanol
Cytospins - acetone	Cytospins - acetone
LBC - ThinPrep	LBC - ThinPrep
LBC- SurePath	LBC- SurePath
Smear - air dried	Smear - air dried
Smear - formalin	Smear - formalin

- Each step in sample preparation can affect IR
- ICC procedure for FFPE and cytology slides not identical
- * analytical protocol for control and the sample should be the same

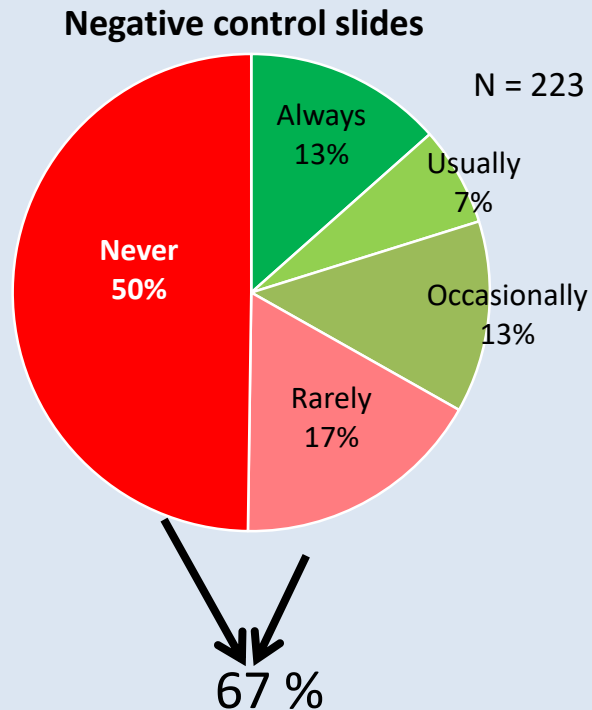
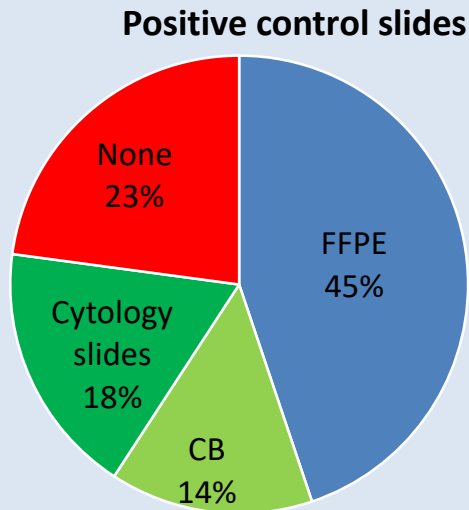
Positive control slides



- enough well distributed cells in monolayer
- positive and negative cell population
- good cell morphology



ICC Controls - European survey



Srebotnik Kirbiš I, Rodrigues Roque R, Bongiovanni M, Strojan Fležar M, Cochand-Priollet B. Immunocytochemistry practices in European cytopathology laboratories-Review of European Federation of Cytology Societies (EFCS) online survey results with best practice recommendations. Cancer Cytopathol. 2020;128(10):757-766.

How to prepare enough good control slides from cytology samples?

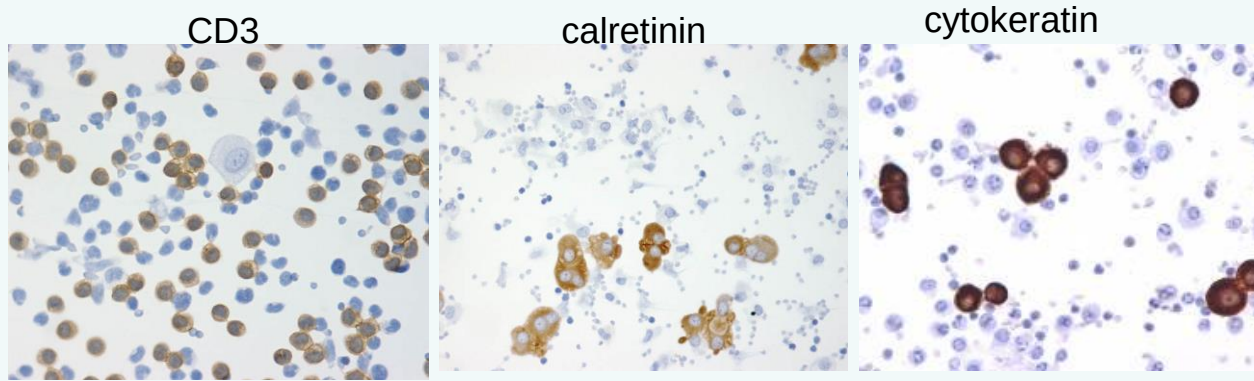
Cytology samples for controls

- leftovers of diagnostic cytology samples
- effusions
- cytology samples (FNA's, brushings) of fresh resected tumours
- human cell lines

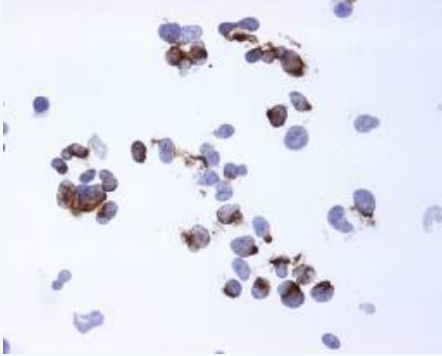


Effusion for controls

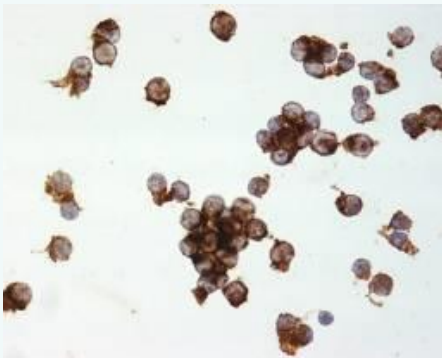
- lymphoid cells (CD3,CD20,CD45)
- mesothelial cells (calretinin, HBME, CK5/6)
- carcinoma cells (cytokeratins, MOC-31)



FNA's of resected tumors

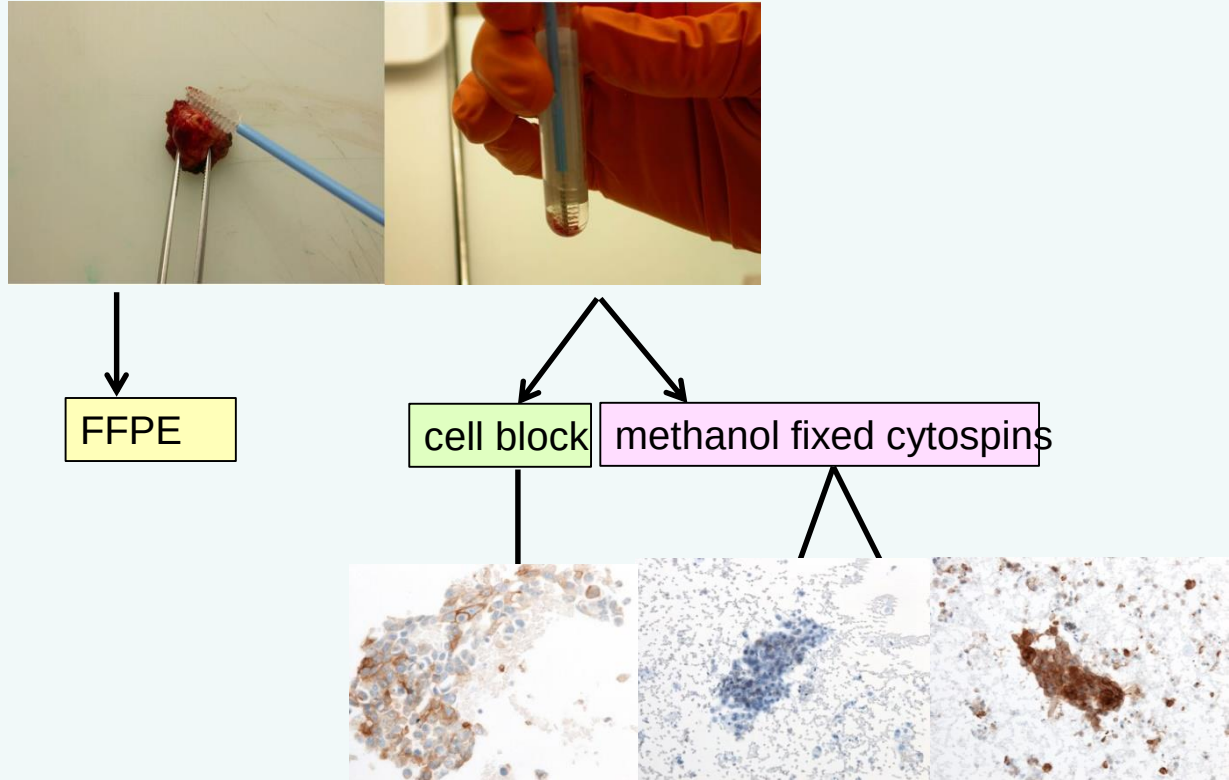


ex-vivo FNAB sample of intra-abdominal **desmoplastic small cell tumour**; **desmin** on Papanicolaou stained cytospin

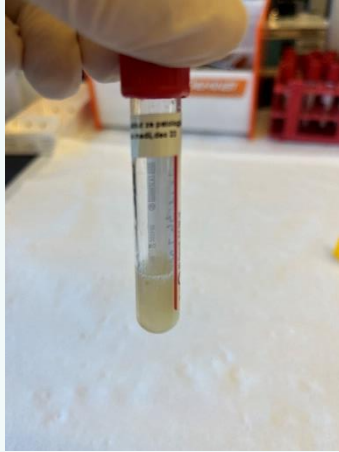


ex-vivo FNAB sample of **thyroid carcinoma**; **thyroglobulin** on Papanicolaou stained cytospin

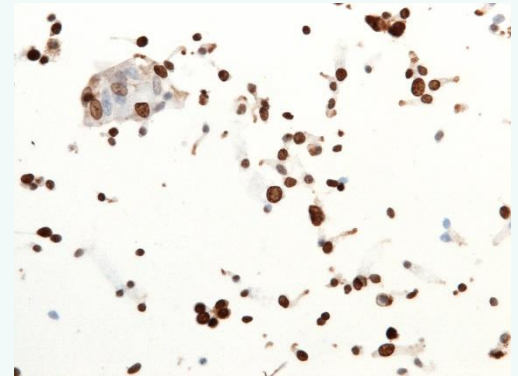
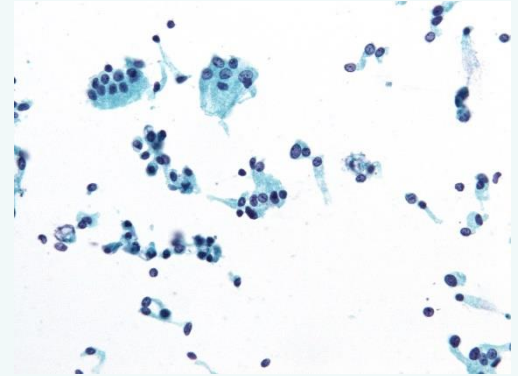
Brushing of resected tumors- PDL1 study



Brushing of fresh tissue – controls SATB2



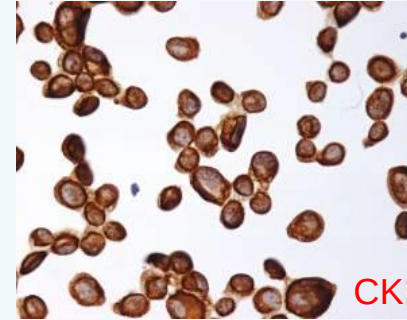
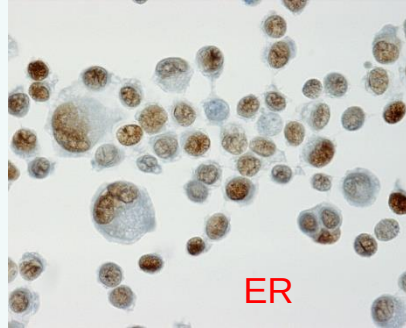
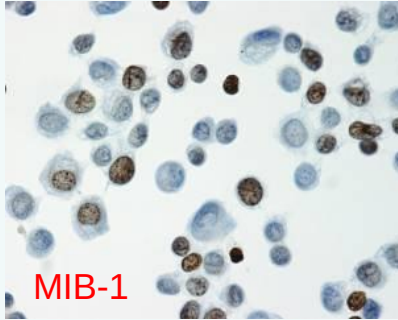
→ 30 cytopsins



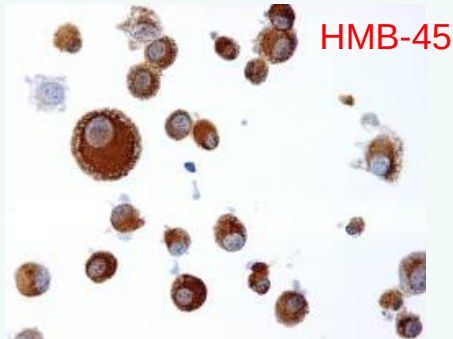
SATB2 on cytopsin

Cell lines for controls

Human breast cancer cell line MCF-7



Human melanoma cell line SK-MEL 28



Good control slides from cytology samples

TEAM work:

- hunt suitable sample
- testing

TIME:

- slide preparation
- analysis (evaluation, comparison)
- documentation

Negative controls

Negative control slides

- Additional slide from diagnostic sample
- Replacing primary antibody with diluent buffer

Check:

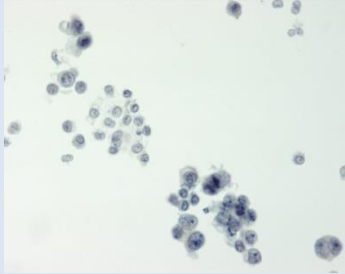
- non-specific staining

Each sample?

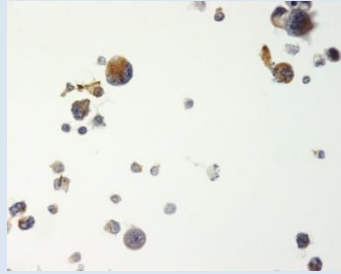
- according to lab experiences
- any change in slide preparation technique
- any change in immunostaining protocol

Negative controls – new detection kit

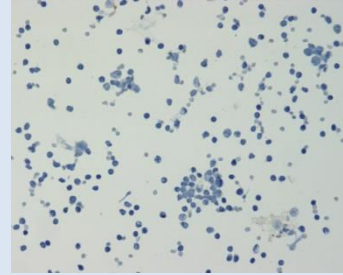
Detection kit 1



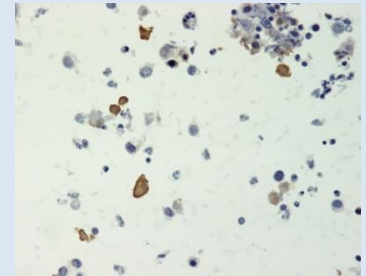
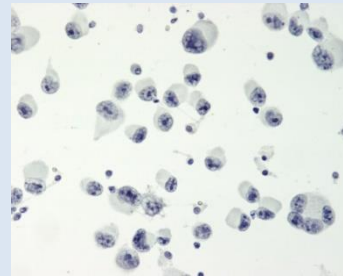
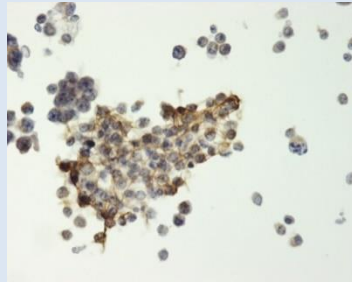
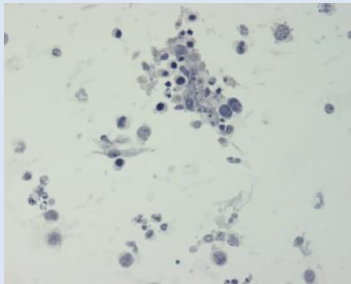
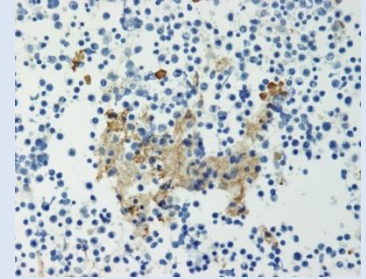
Detection kit 2



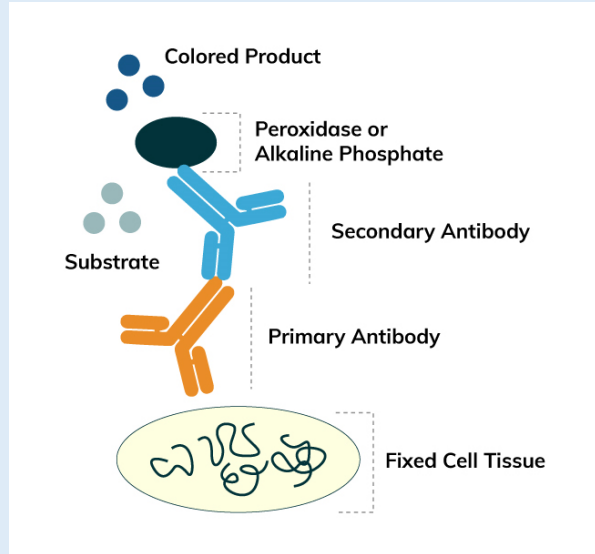
Detection kit 1



Detection kit 2



Optimization and validation



Antibodies for IHC detect epitopes in FFPE!

Each modification/variation from standard FFPE should be validated

Quality Assurance For Immunocytochemistry: Approved Guideline, Clinical Laboratory Standards Institute (formerly NCCLS), Wayne PA, USA, publication MM4-A, Vol. 19, No. 26, 1999. www.clsi.org

Optimization and validation

Optimization – adjustment of steps in ICC procedure

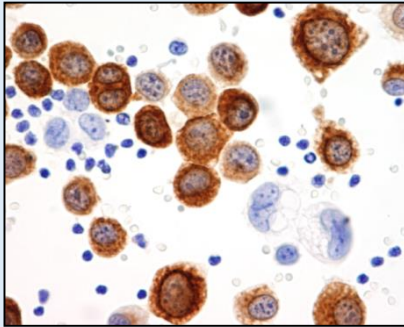
Validation – reliable, correct, results

Basic requirements

- Adequate positive controls
- **Assessment of ICC quality!**

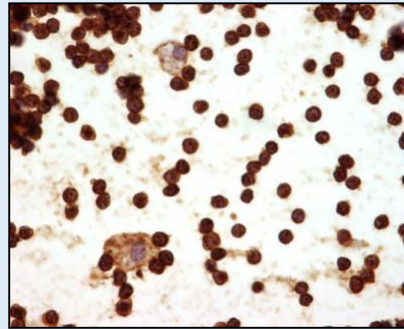
Quality of ICC

Optimal quality ICC

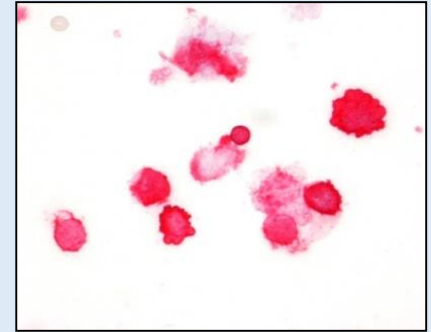


- properly localized
- clearly visible
- specific
- well preserved cell morphology
- no background

Poor quality ICC



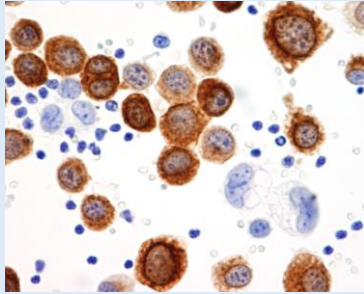
- poor cell morphology
- non specific staining
- background



Discrepancy in perception of immunocytochemical staining quality

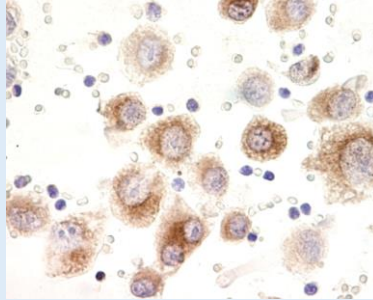
HMB-45 on identical UK NEQAS slides

Lab 1



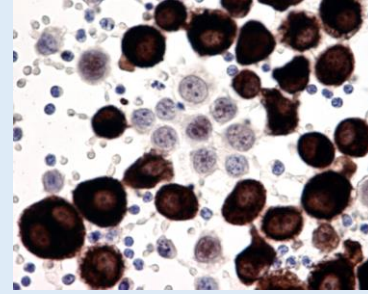
Very good
Very good

Lab 2



Very good
Borderline

Lab 3



Very good
Borderline

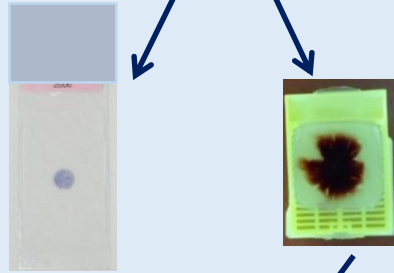
In house assessors
External assessors

Basic assessment scores(1-5)

Score	Description	Interpretation
5	Excellent	No improvements are required.
4	Good	Minor improvements are possible.
3	Adequate/Sub-optimal- clinically safe	Weak demonstration of antigen, below the expected level. Non-specific and/or inappropriate staining is present but does not make the staining uninterpretable. Some morphological damage caused by excessive pretreatment. Poor tissue/section quality. Excessive or very weak haematoxylin counterstain.
2	Poor/Sub-optimal -clinically unsafe	Clinically uninterpretable. Staining has no utility. Improvement essential.
1	Inadequate	Clinically uninterpretable. Staining has no utility. Improvement essential. No significant demonstration of requested antigen.

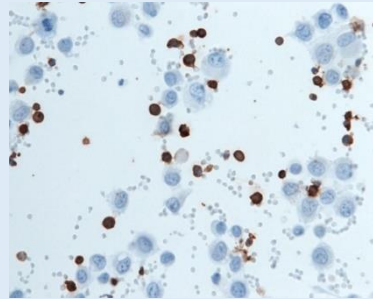
Run 108 – CD45, melanoma

- Human melanoma cell line SK-MEL28
- Effusion with carcinoma cells, few mesothelial cells, Erci
- FNAB of lymph node

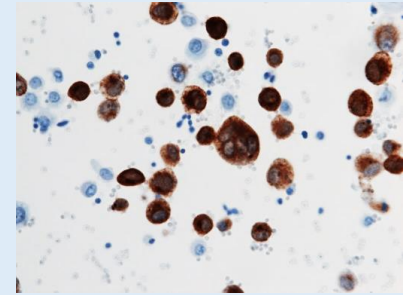


CD45, HMB-45, MelanA, S-100

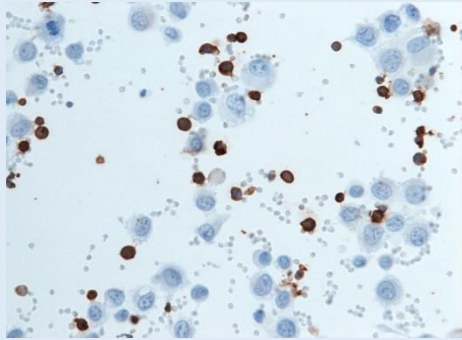
CD45



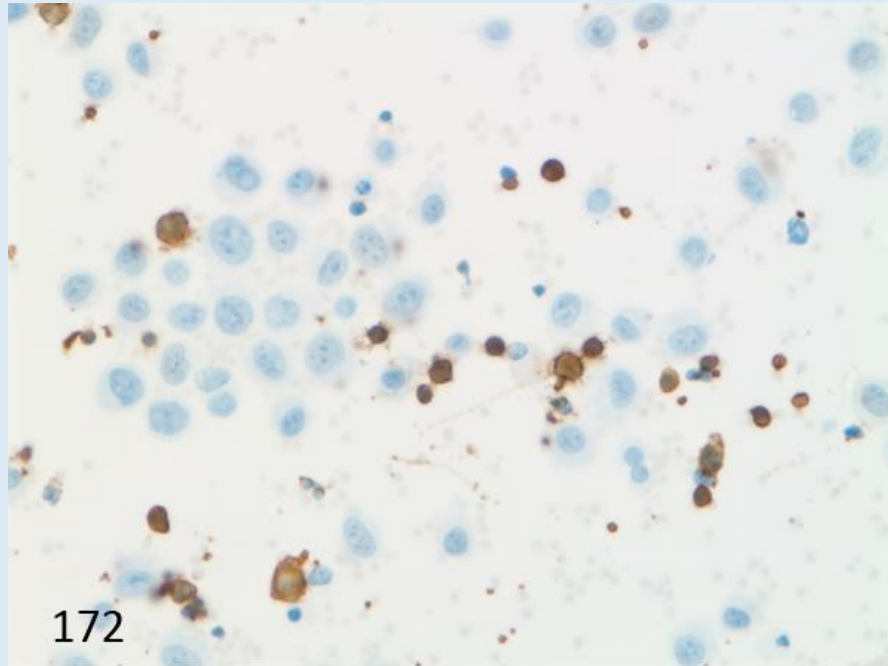
HMB-45



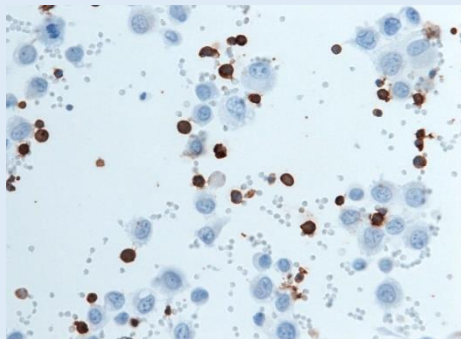
CD45



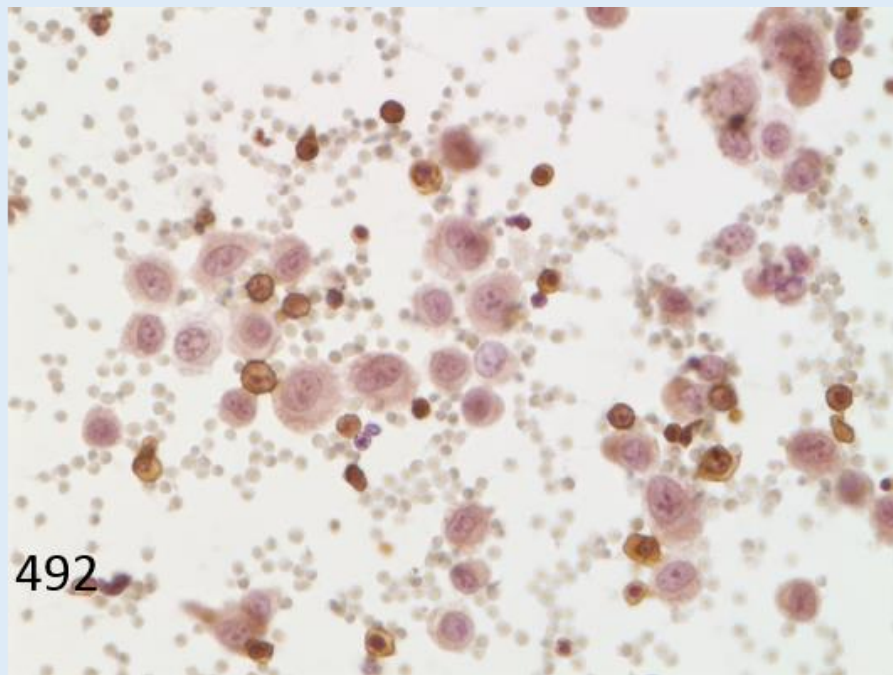
LAB 172 (CD45) - cytospin



5+5+5+5=20

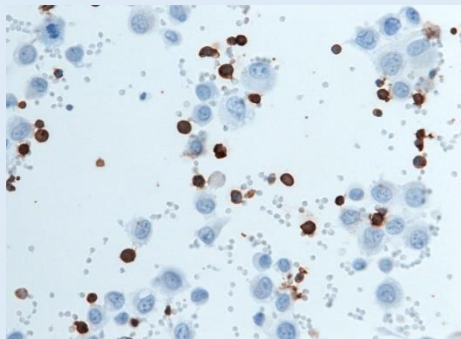


LAB 492 (CD45) - cytospin

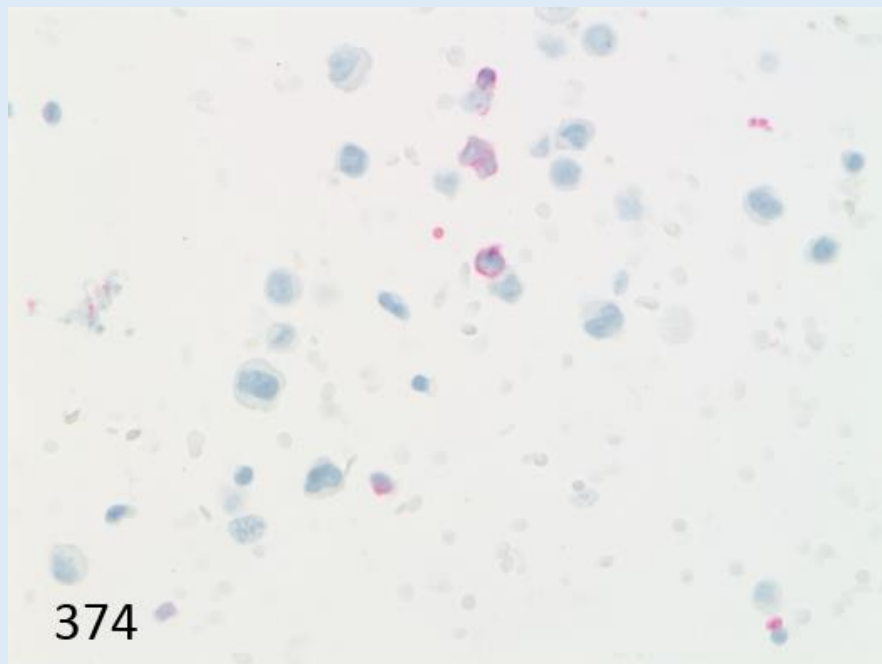


492

$$2+3+2+2= \mathbf{9}$$



LAB 374 (CD45) - cell block



$$3 + 3 + 3 + 3 = 12$$

Optimization of IHC/ICC protocols

Optimization – adjusting steps in IHC/ICC staining procedure yielding the best ratio between specific/nonspecific staining

ICC protocols $\neq$ IHC protocols

ICC protocols $\neq$ IHC protocols

Our optimization

- Cytospins fixed in methanol
- 39 antibodies

Step	ICC	IHC
Deparaffination	no	yes
H2O2/methanol	yes	no
Antigen retrieval	1/39 (2 %)	38/39 (97 %)
iView	34/39 (87 %)	2/39 (5 %)
ultraView	4/39 (10 %)	32/39 (82 %)
optiView	0	4/39 (10 %)
Antibody dilutions ICC : IHC	 27/39 (69 %) = 12/39 (31 %)	

ICC protocols ≠ IHC protocols

- Cellient cell blocks - adapted IHC protocol for 15/30 antibodies
 - LBC: FFPE from the same sample - 10 % Ab non reactive/inconsistent on LBC using IHC protocols
 - Thrombin CB : Cellient CB (70 samples)- Cellient CB - modified FFPE protocol (43 %)
-
- Sauter et al. Validation and Optimization of Immunohistochemistry Protocols for Use on Cellient Cell Block Specimens. Cancer (Cancer Cytopathol) 2016;124:89-99.
 - Sauter JL, Ambaye AB, Mount SL. Increased utilization, verification, and clinical implications of immunocytochemistry: Experience in a northern New England hospital. Diagn Cytopathol 2015;43(9):688-95.
 - Sauter JL, Grogg KL, Vrana JA, Law ME, Halvorson JL, Henry MR. Young investigator challenge: Validation and optimization of immunohistochemistry protocols for use on cellient cell block specimens. Cancer Cytopathol. 2016;124(2):89-100.

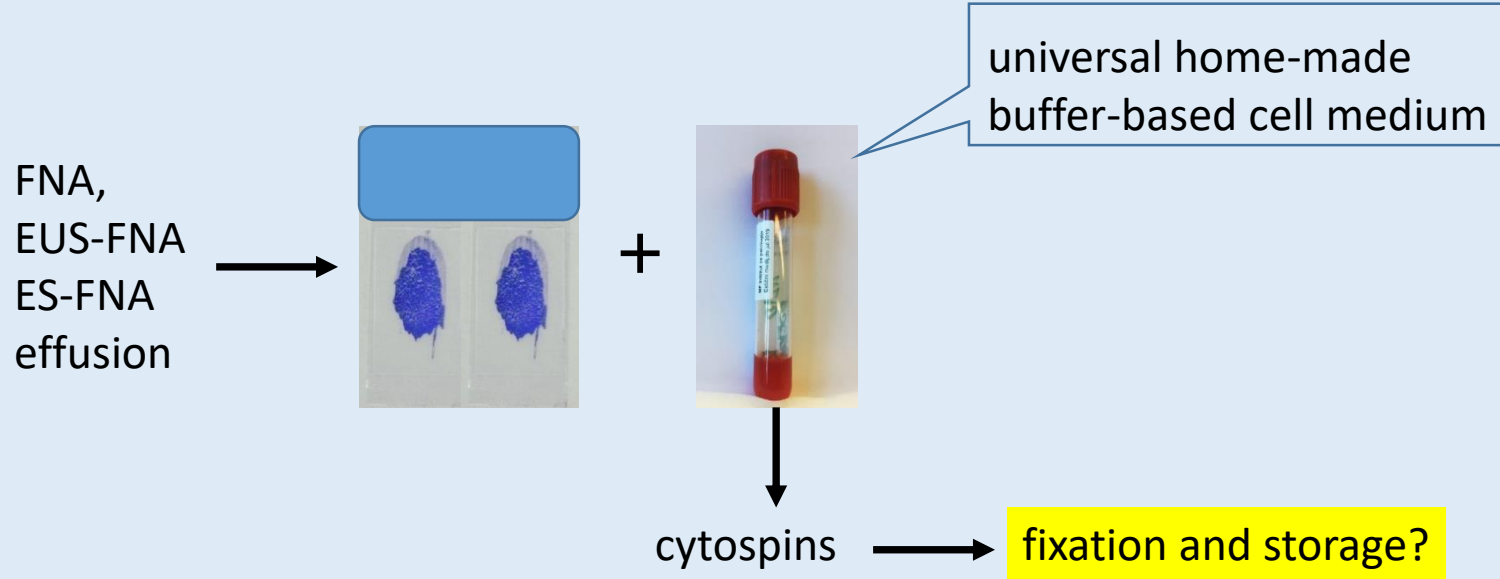
Validation

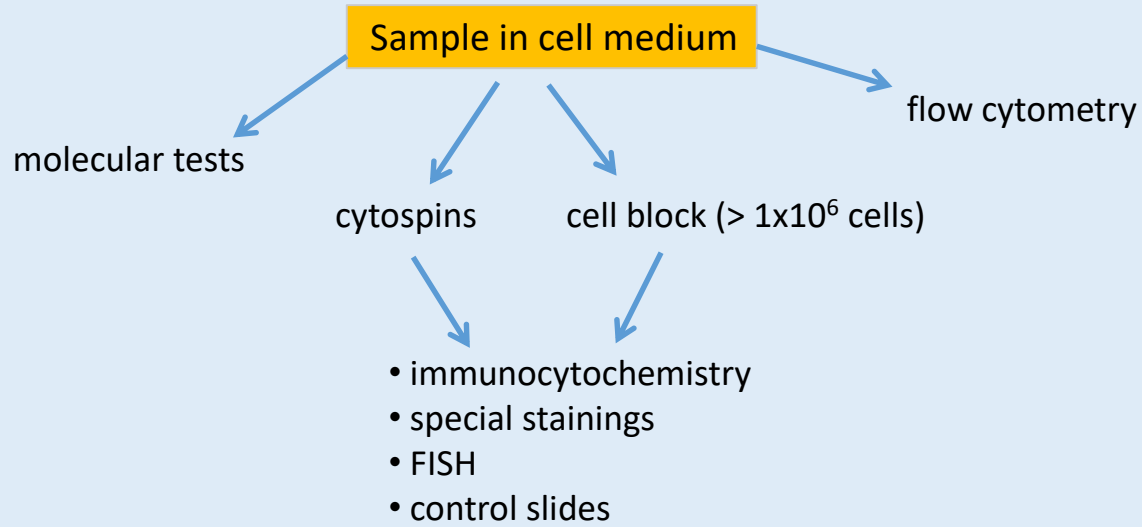
- Validation ensures a test works as intended. Any antibody assay (novel or replacement) must be validated before it is put into use as a diagnostic test.
- Objective evidence that test performs reliable and consistently - accurate, correct, reliable results

ICC : IHC/flow cytometry immunophenotyping/....

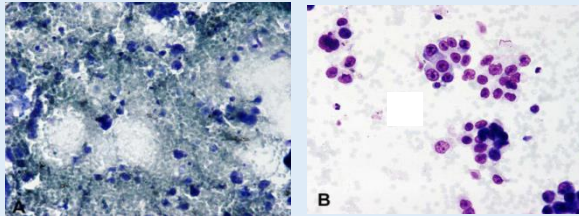
- **Quality Assurance For Immuncytochemistry: Approved Guideline**, Clinical Laboratory Standards Institute (formerly NCCLS), Wayne PA, USA, publication MM4-A, Vol. 19, No. 26, 1999. www.clsi.org
- College of American Pathologists

Validation of ICC on cytopins – our approach

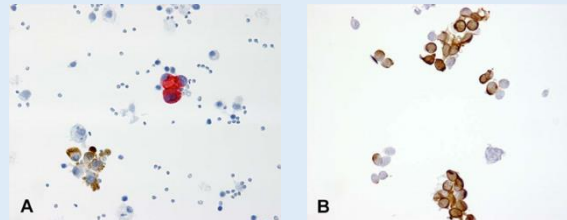




Hemorrhagic sample After filtration



ICC



Validation of ICC

- Optimal fixation for **CD markers** (ICC : IHC: flow cytometry)
- Optimal fixation for **Ki67** (ICC: S-phase)
- Optimal fixation for **ER** (MCF-7 cell line, ICC:IHC)

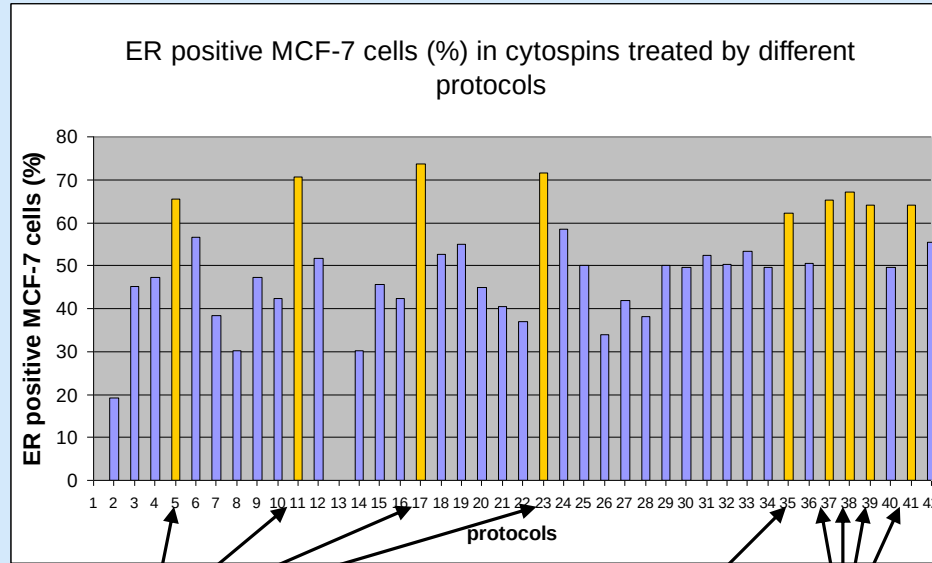
ER optimization and validation

Optimal protocol set-up on MCF-7 cell line

Evaluation of protocols on ex-vivo FNAB samples

Introduction of automated immunostaining

Follow up - response to hormonal treatment



Papanicolaou stained, **Mw10, D100**

5: Delaunay 1hr

11: 96 % ethanol 1hr

17: Delaunay 12 hrs

23: 96 % ethanol 12 hrs

CellFix
Mw10, D100

Methanol

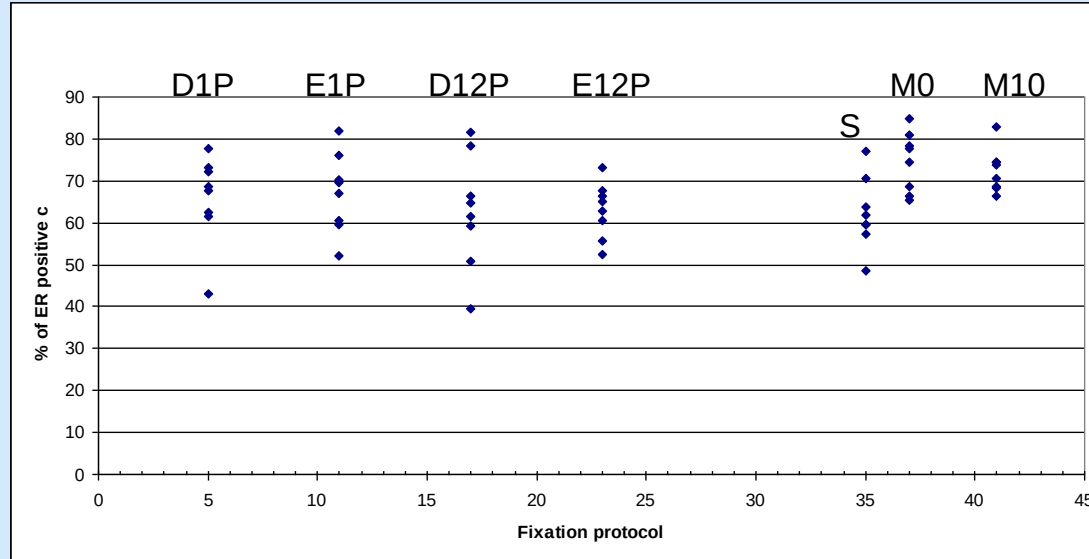
37: Mw 0, D100

38: Mw 0, D200

39: Mw 5, D100

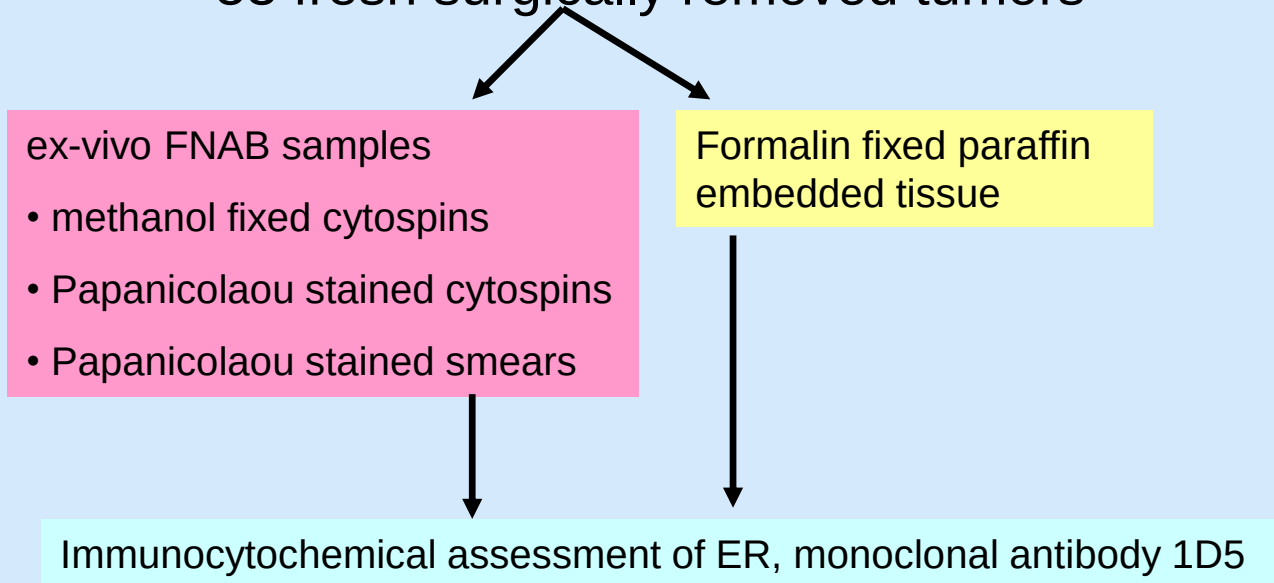
41: Mw 10, D100

Variability in ICK detection of ER positive MCF-7 cells



Protocol evaluation on ex-vivo FNAB samples

53 fresh surgically removed tumors

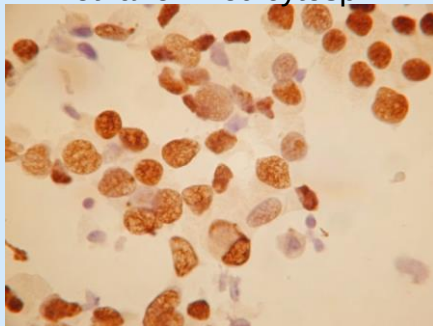


ER on ex-vivo FNAB samples - concordance with corresponding tissue sections

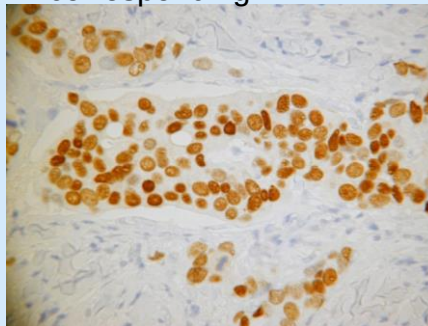
	concordance	kappa
Papanicoalou stained smears	92 %	0.75
Papanicoalou stained cytopspins	94 %	0.84
methanol fixed cytopspins	100 %	1.00

ER assessment

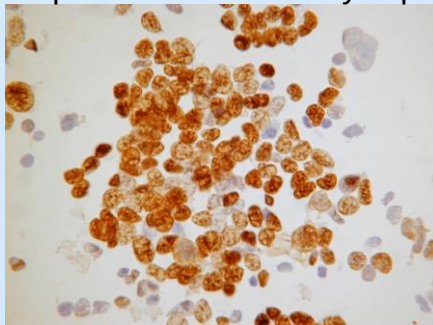
methanol-fixed cytopsin



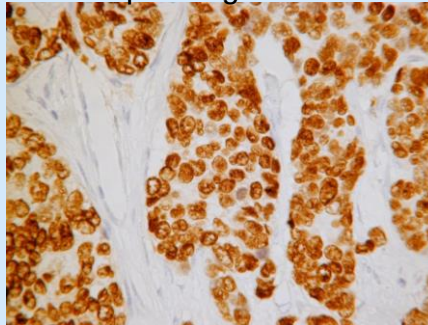
corresponding FFPE



Papanicolaou stained cytopsin



corresponding FFPE



Validation of ICC on cytopins

- Optimal fixation for **CD markers** (ICC : IHC: flow cytometry)
- Optimal fixation for **Ki67** (ICC: S-phase)
- Optimal fixation for **ER** (MCF-7 cell line, ICC:IHC)

} Methanol

Kirbis IS, Flezar MS, Krasovec MU. MIB-1 immunostaining on cytological samples: a protocol without antigen retrieval. Cytopathology. 2004;15(3):154-159. doi:10.1111/j.1365-2303.2004.00146.x

Srebotnik Kirbiš I, Us Krašovec M, Pogačnik A, Strojan Fležar M. Optimization and validation of immunocytochemical detection of oestrogen receptors on cytopins prepared from fine needle aspiration (FNA) samples of breast cancer. Cytopathology. 2015;26(2):88-98. doi:10.1111/cyt.12143

Srebotnik Kirbis I, Prosen L, Strojan Flezar M. Time-related changes in cell morphology and biomarker immunoreactivity for cells stored in a buffer-based cell medium. Cytopathology. 2021;32(4):513-518. doi:10.1111/cyt.12980

Validation of ICC

38 other markers:

- positive controls with known/expected expression
- methanol preserve all tested antigens

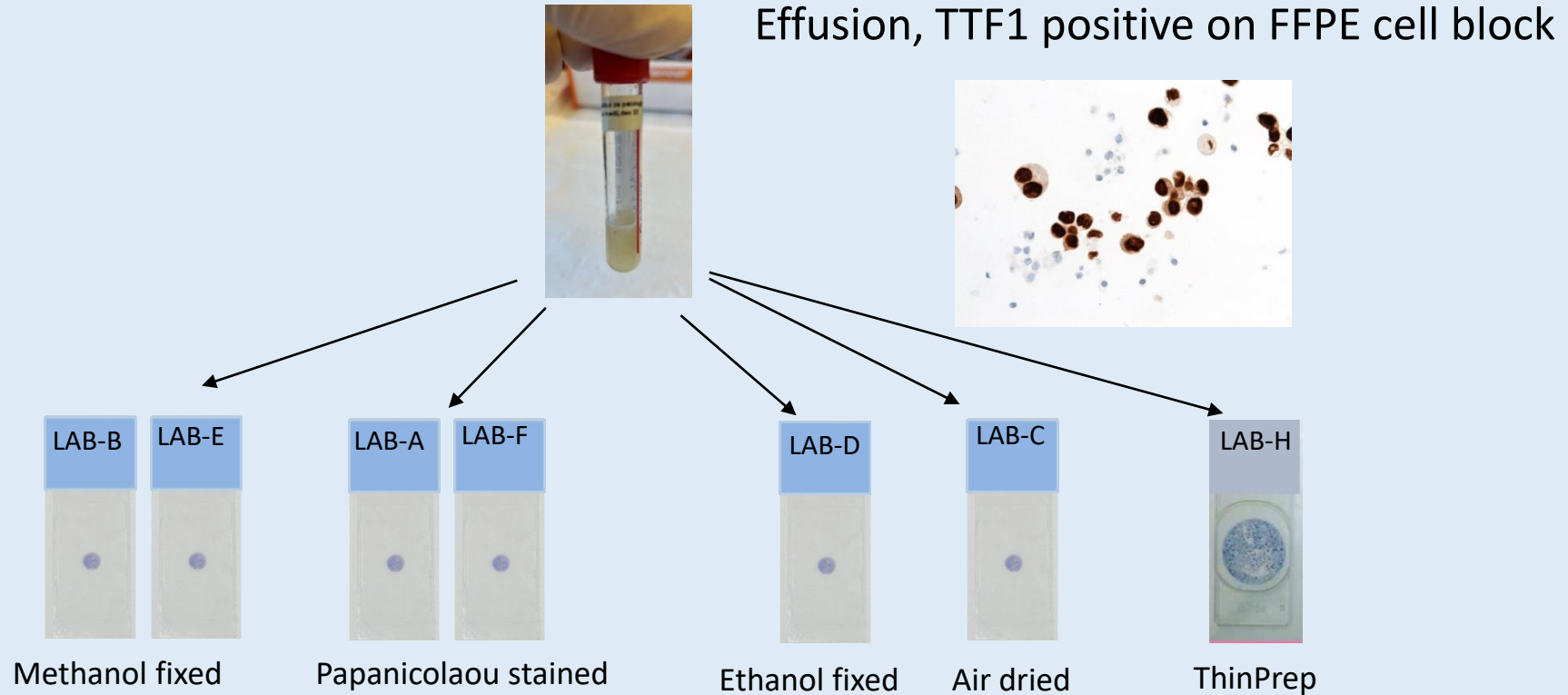
Validation of ICC

50 diagnostic routine cytology samples

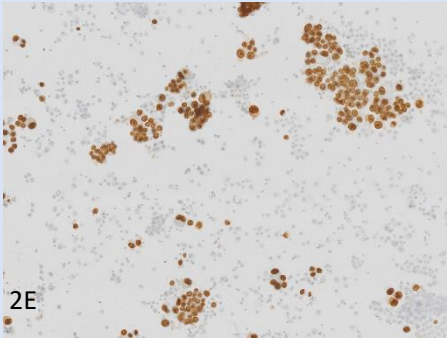
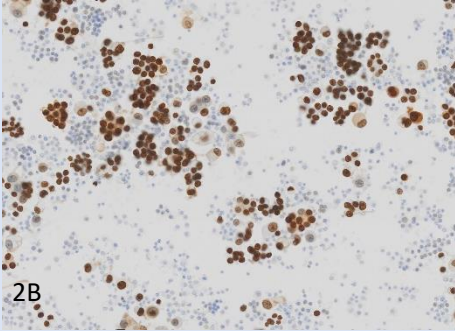
ICC on methanol fixed cytopins : IHC on concordant FFPE

IHC	ICC		
	Neg	Poz	Together
Neg	67	0	67
Poz	5	74	79
Together	72	74	146
Concordance	141/146, 97 %, $\kappa = 0,93$		

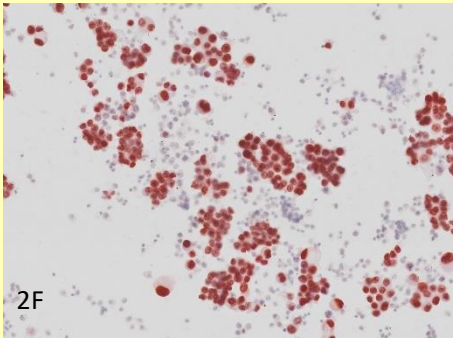
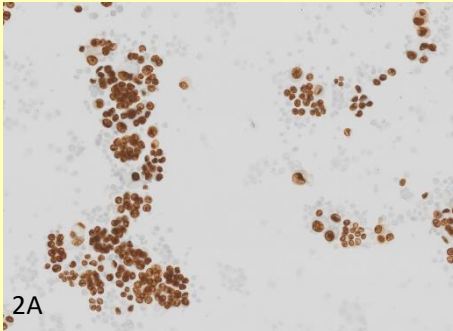
Interlaboratory ICC comparison – Cytology WG project of the IASLC Pathology Committee



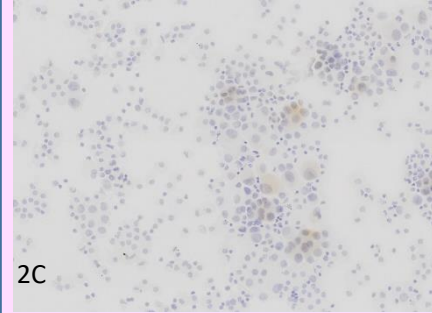
Methanol



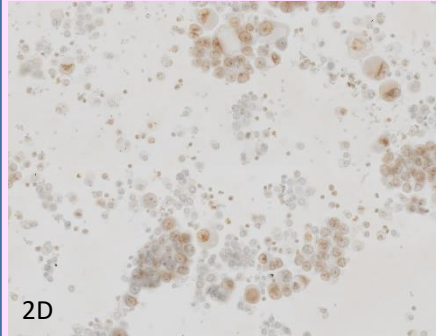
Papanicolaou



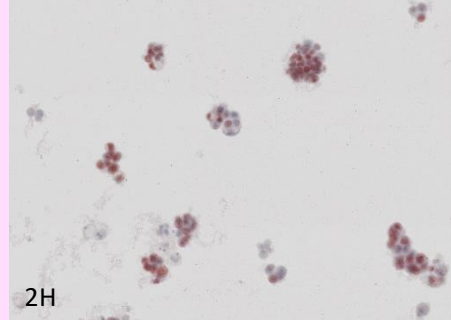
Air-dried



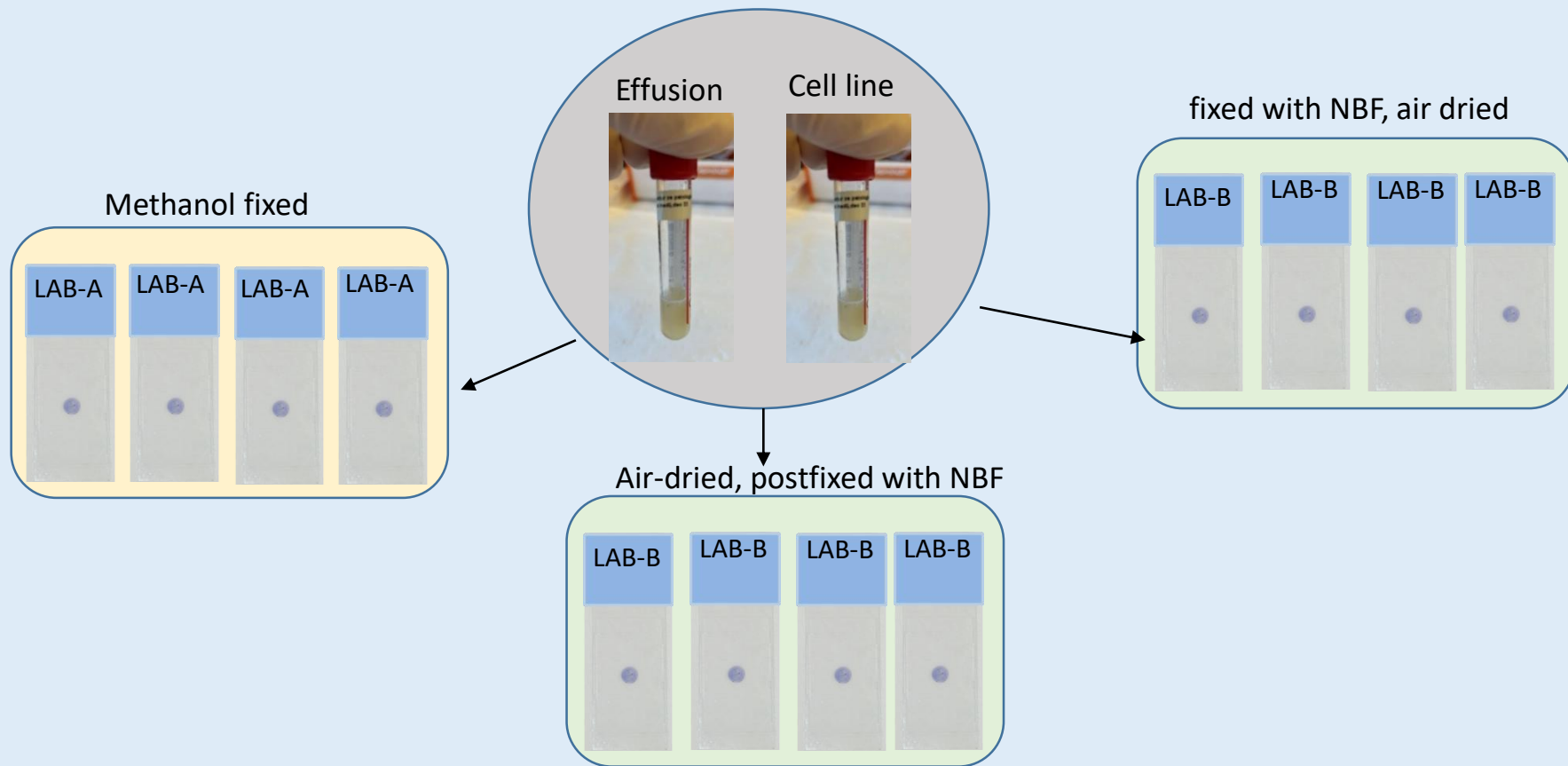
Ethanol



ThinPrep



Interlaboratory ICC comparison – methanol:NBF

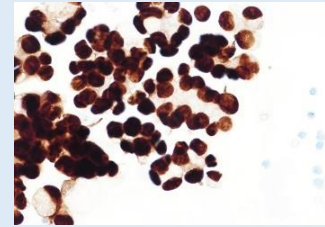
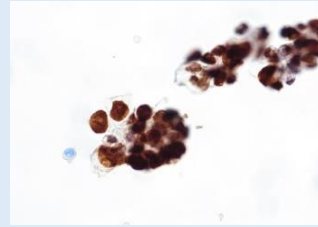
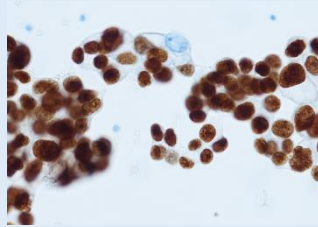


Methanol

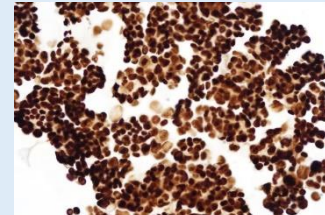
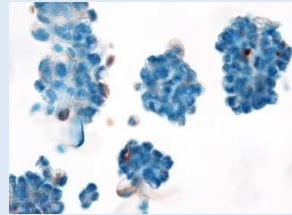
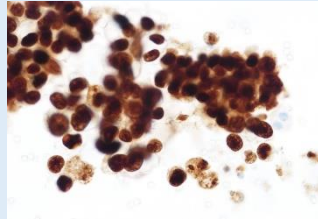
NBF

Air-dried, NBF post-fixed

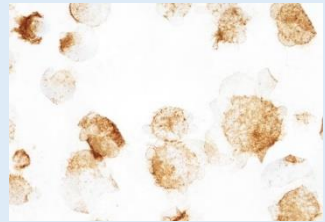
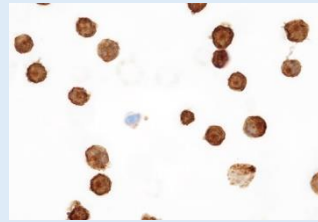
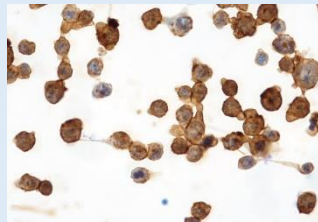
PAX8



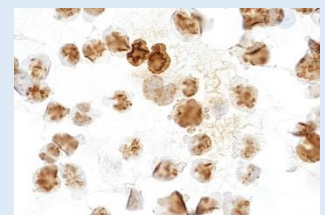
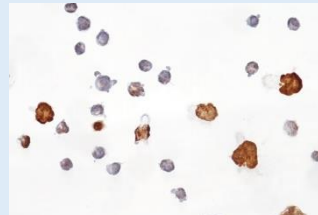
p53



CD20



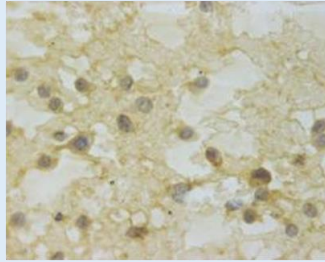
Ki67



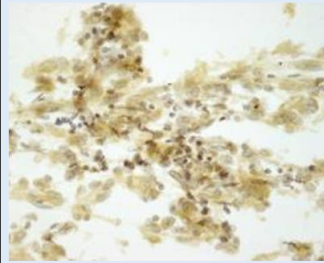
Development of sample processing

1988
Direct smears

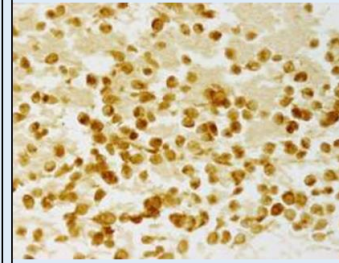
CK



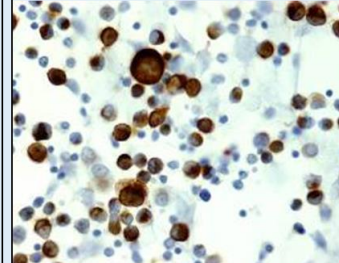
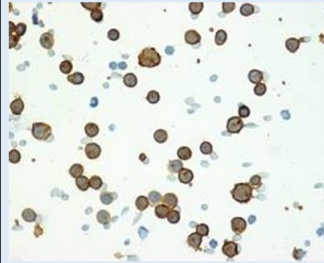
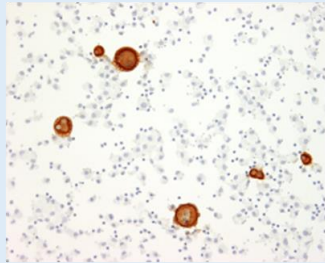
CD45



DES



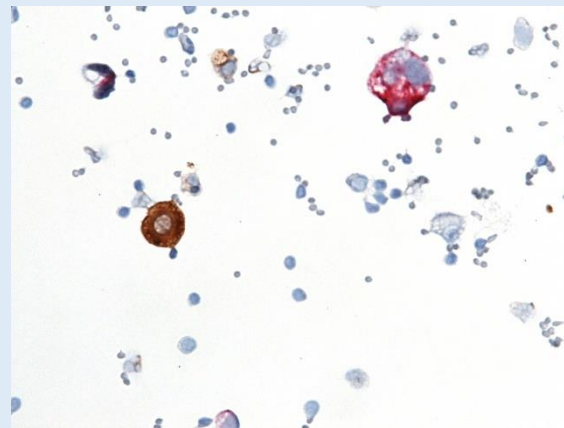
2008
Cytospins



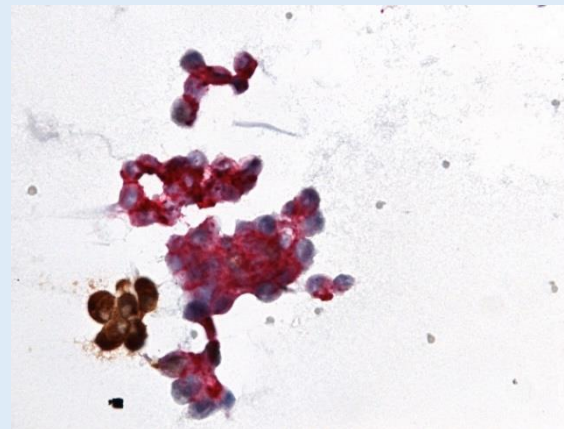
Integrated on-slide controls



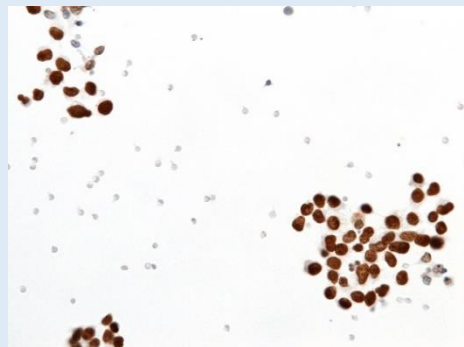
Patient sample



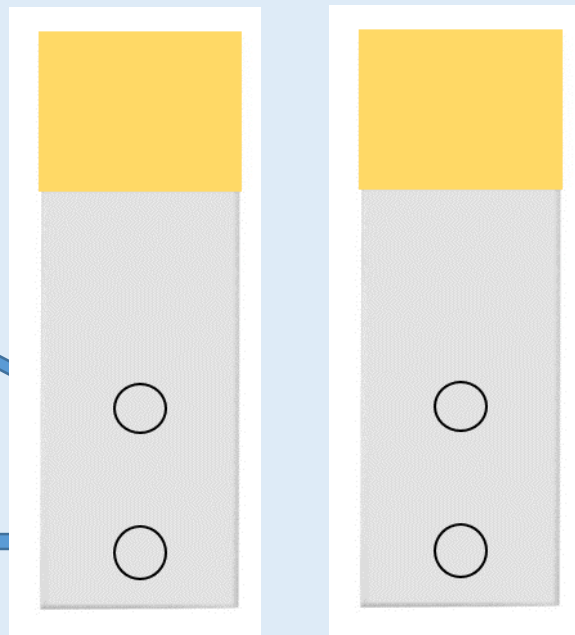
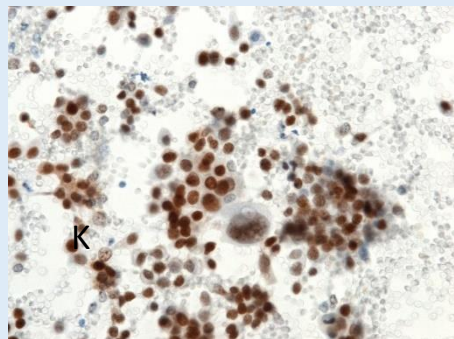
Integrated control



ER

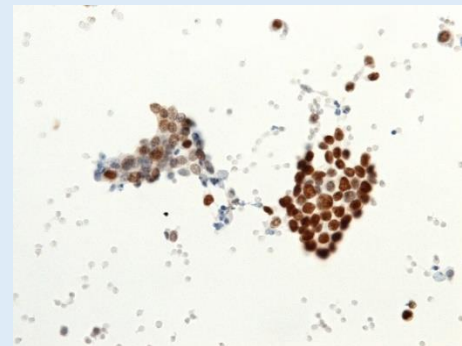


Patient
sample

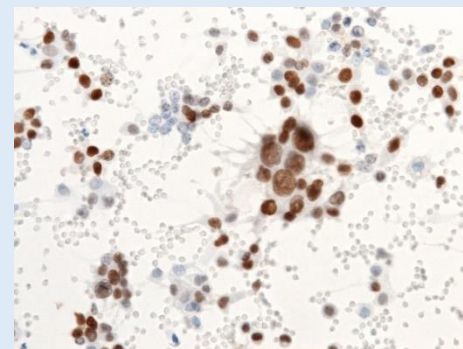


Integrated positive control

PR

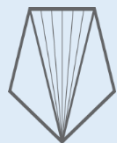


Patient
sample



Conclusions

- The value of cytology in a modern personalized medicine
 - Quick, efficient, minimally invasive
 - First line, monitoring
 - Deep-seated lesions
- Specifics of cytology samples
 - Small samples, non-standardized processing
- Biomarker testing on cytology samples
 - Optimization, validation , EQA, recommendations



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