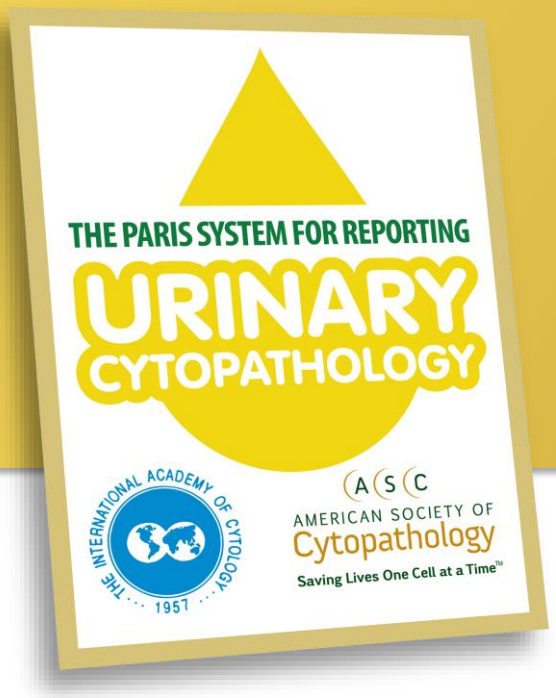
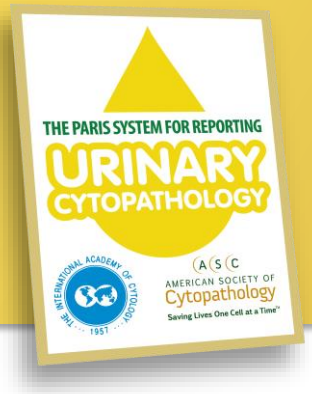
The Paris System for Reporting Urinary Cytopathology

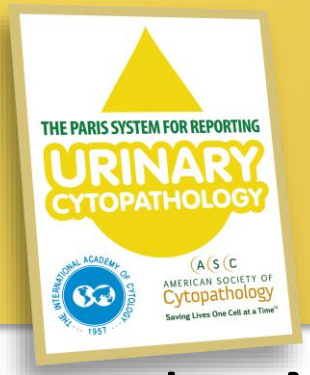


Dr Ashish Chandra
MD FRCPath DipRCPath (Cyto)
Guy's & St. Thomas' NHSfT
London, UK



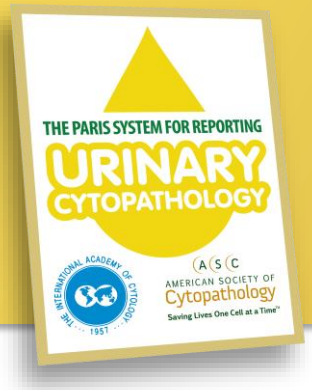
The Paris System (TPS) for reporting urinary cytopathology

- Joint initiative of the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC)
- Led by Dr Dorothy Rosenthal (Johns Hopkins, Baltimore) and Dr Eva Wojcik (Loyola, Chicago)
- Further developed by members of the ASC and IAC at the International Congress of Cytology meeting held in Paris in May 2013
- Echoes Bethesda terminology for reporting cervical and thyroid cytology



TPS: Categories

- I. Non-diagnostic or Unsatisfactory
- II. Negative for High Grade Urothelial Carcinoma
- III. Atypia
- IV. Suspicious for High Grade Urothelial Carcinoma
- V. Low Grade Urothelial Neoplasia (LGUN)
- VI. High Grade Urothelial Carcinoma (HGUC)
- VII. Other malignancies, primary and metastatic

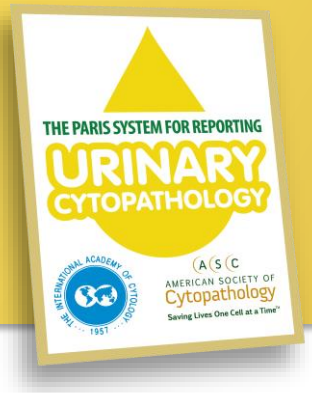


Histopathological terminology of urothelial neoplasia

- **WHO 1973:** Grades 1, 2 and 3
- **ISUP/WHO 2004:** Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

  Low grade urothelial carcinoma (LGUC)

  High grade urothelial carcinoma (HGUC)
- Use of the term carcinoma for low grade tumours (PUNLMP & LGUC) needs revision
- *The Paris system of reporting urinary cytology is leading the way in guiding histopathological terminology of urothelial neoplasia*

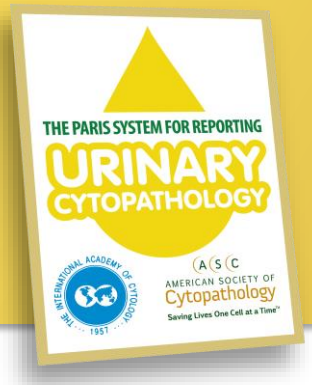


I. Non-diagnostic or Unsatisfactory

- Cellularity and cell content varies widely
- Unsatisfactory or unsuitable when sample quality is compromised due to degenerative changes due to overgrowth of contaminant microbes or cells obscured by blood, exudate or other artefacts
- 20 cells/10 hpf in bladder washings (LBC). JASC 2015,4;57-62

Evidence-based Adequacy Criteria for Bladder Cytology

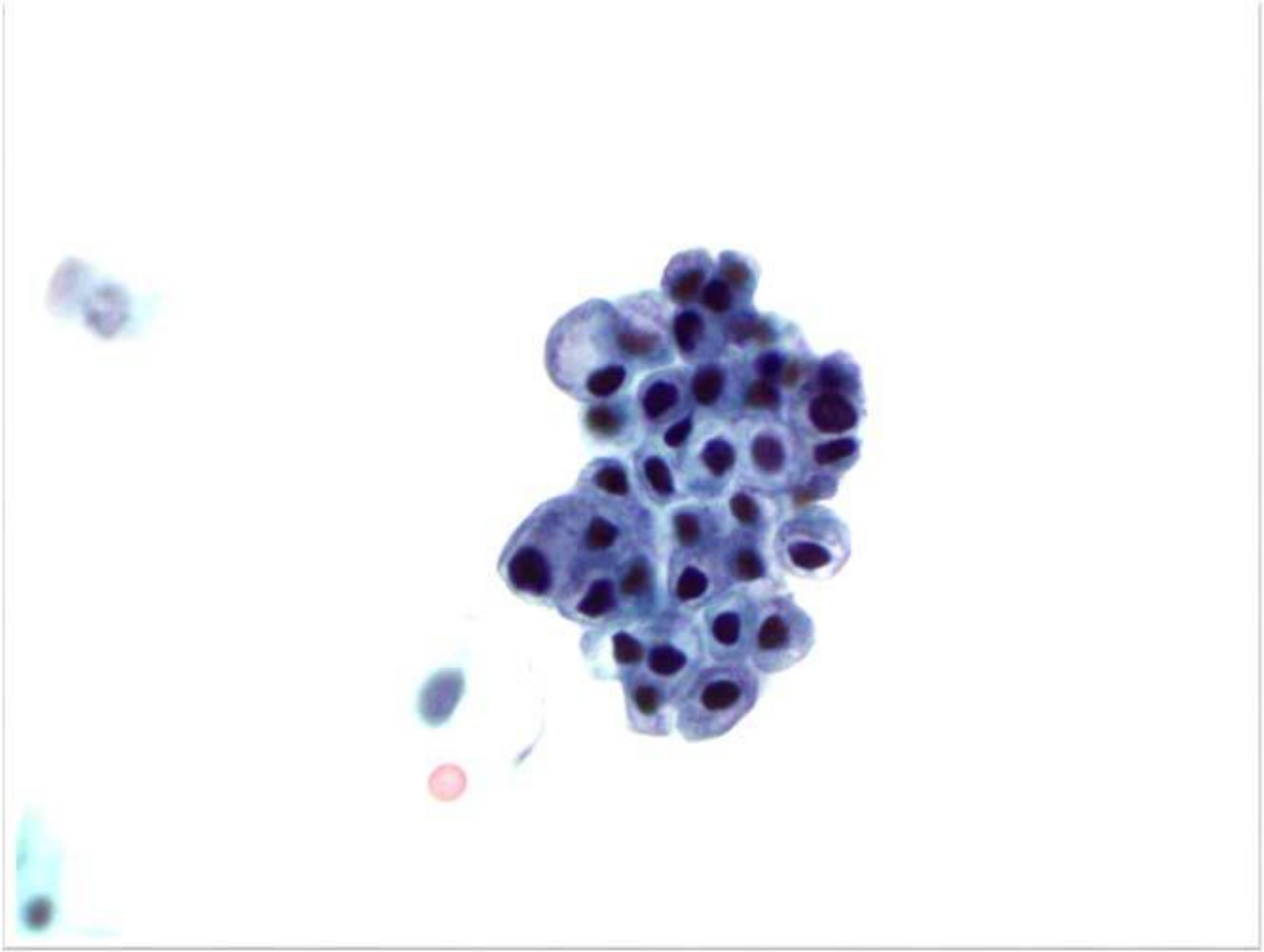
Jennifer Prather, MD, Brent Arville, DO, Grazina Chatt, CT(ASCP), Stefan E. Pambuccian, MD, Eva M. Wojcik, MD, Güliz A. Barkan, MD
Loyola University Medical Center, Chicago, Illinois



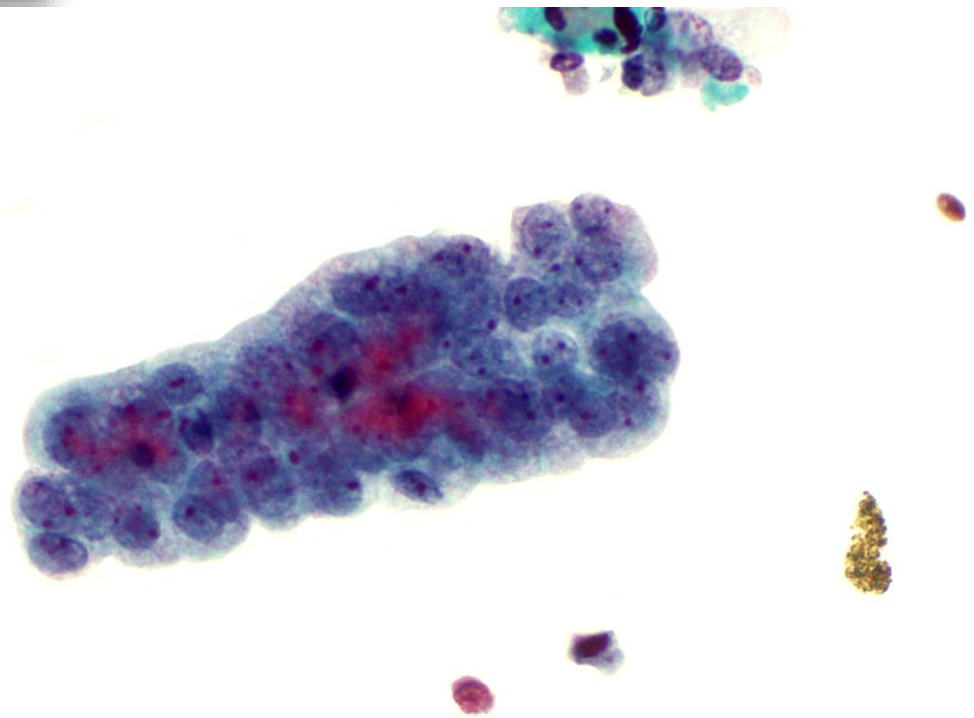
II. Negative for HGUC

- Implies absence of atypical, suspicious or malignant cells in an adequate sample
- Features attributable to inflammation may be referred as 'reactive changes' but reported as negative for HGUC. The word 'atypia' should not be used in this setting
- Treatment effect and BK virus effect may be reported as Negative for HGUC

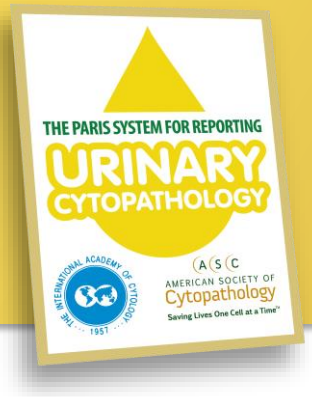
Negative for high grade urothelial carcinoma



Reactive Urothelial Cells (Negative for HGUC)

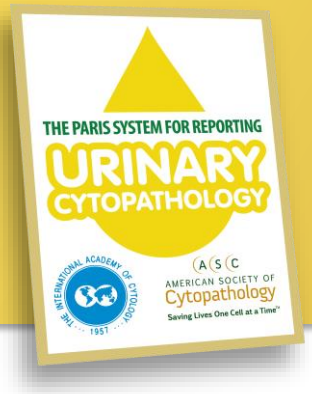


- Uniform size
- Fine chromatin
- Round nuclei
- Smooth borders
- Small nucleoli



III. Atypia

- Atypia should be reminiscent of HGUC but in very small numbers
- Does not include papillary clusters suggestive of LGUN



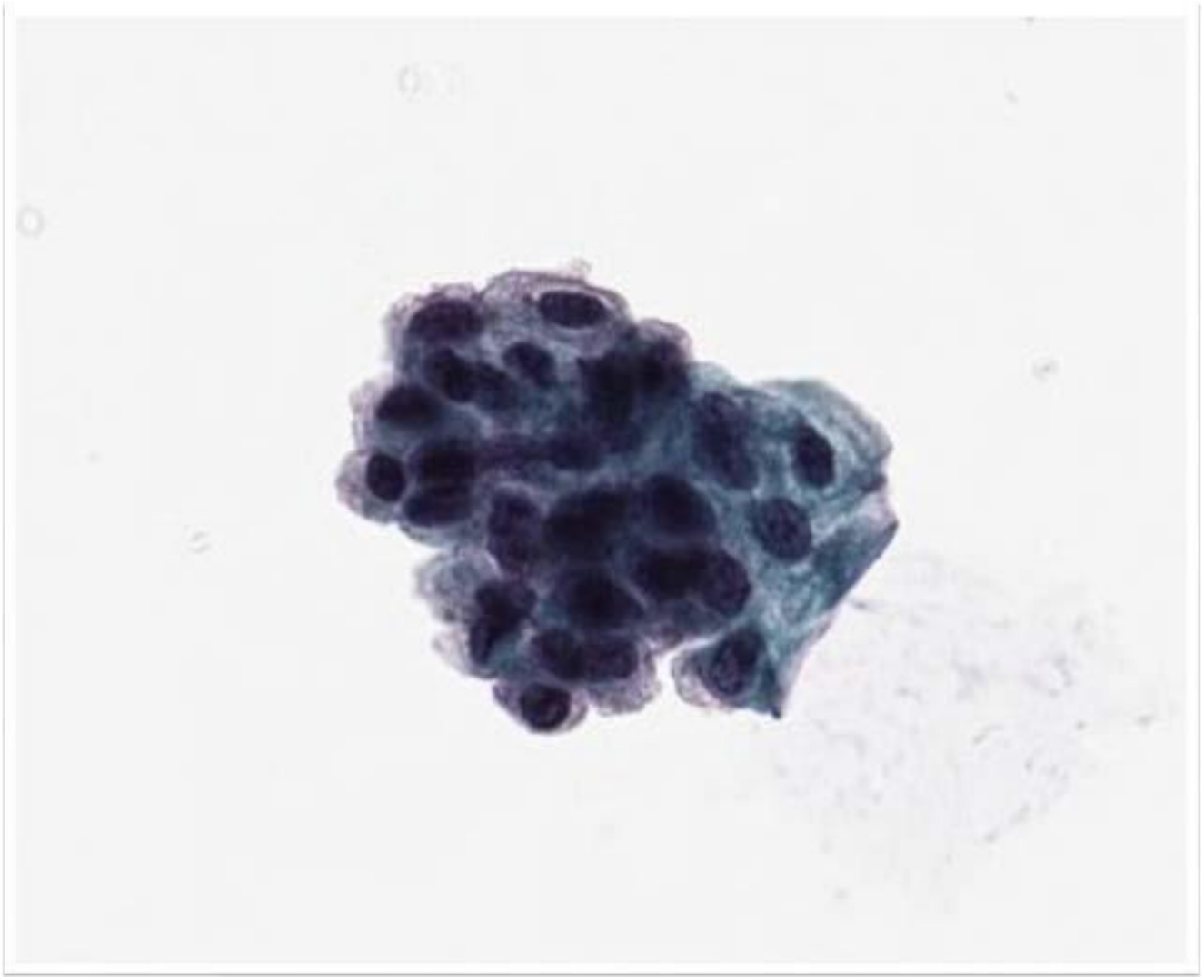
Criteria for Atypia

- Non-superficial and non-degenerated urothelial cells with a **high N/C ratio > 0.5 (required)**

  and one of the following:

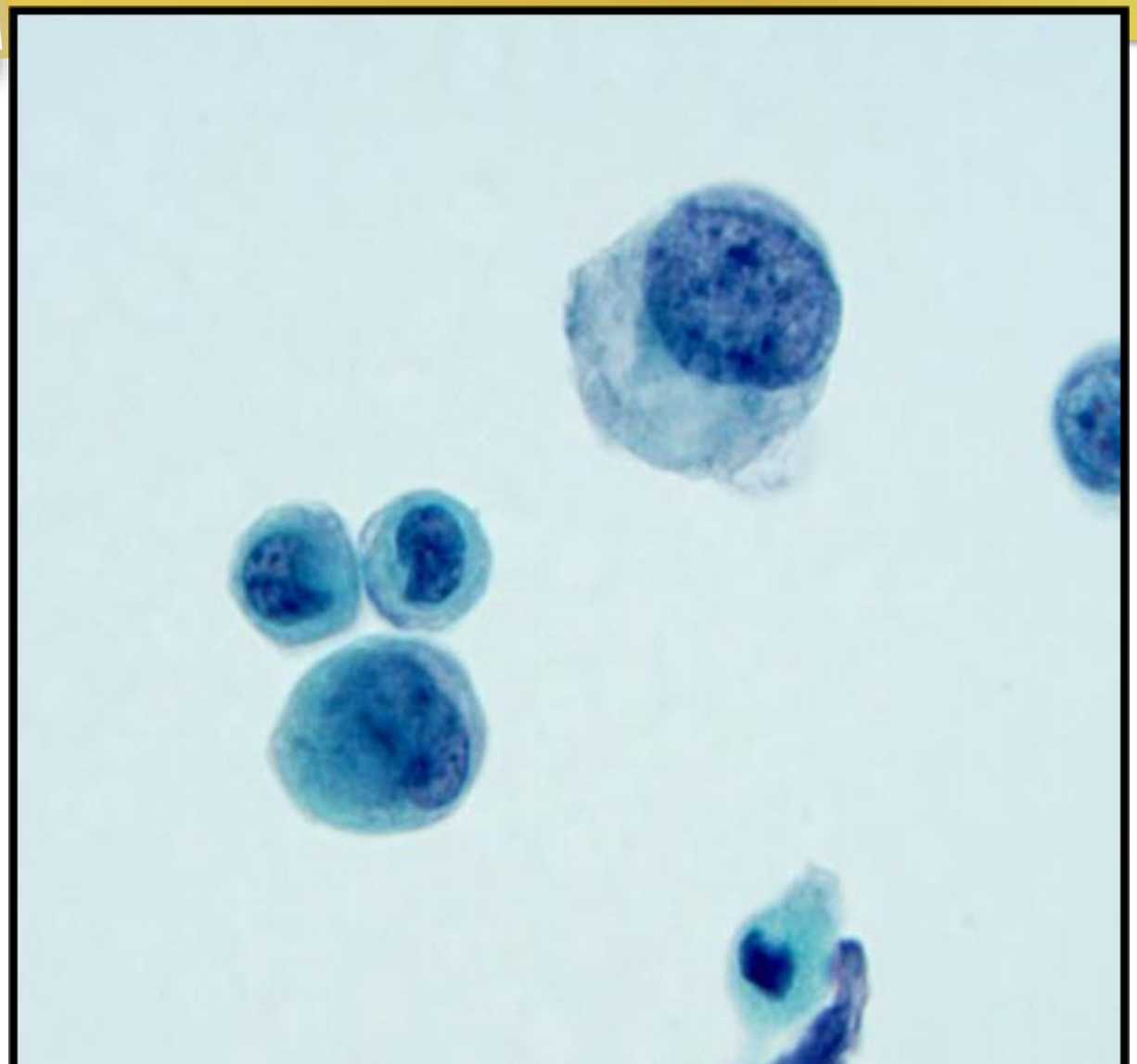
- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus)
- **Irregular clumped chromatin**
- **Irregular nuclear membranes**

Atypia



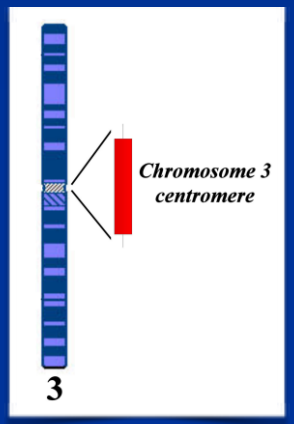
Atypia

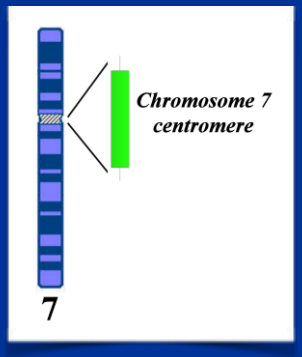
Atypia

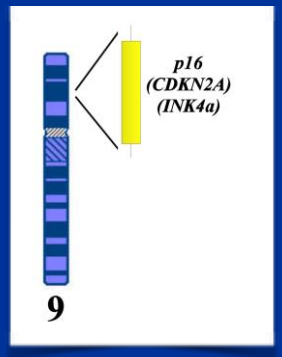


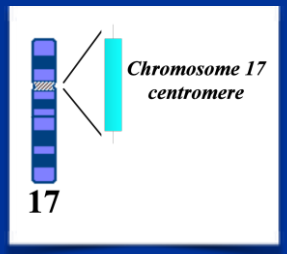
Atypical cytology and ancillary testing: UroVysion FISH

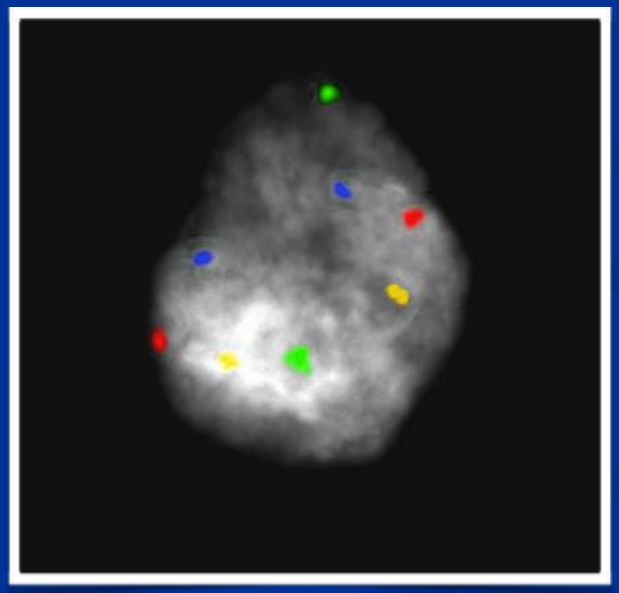
Mix of 4 probes labelled with fluorochromes











Courtesy: Dr Michael Neat, Chief Cytogeneticist, Viapath, London

Analysis and criteria for classification of UroVysion FISH results

- **Initially select morphologically abnormal cells**
  - Large nuclear size/irregular shape
  - Patchy DAPI stain
  - Cell clusters (non-overlapping)
  - If no morphologically abnormal cells present, scan all cells
- **Minimum analysis of 25 cells**
- **FISH positive if:**
  - **≥4 cells showing gain of at least 2 of #3, #7 & #17**
  - **≥12 cells showing homozygous deletion of *p16* i.e. no *p16* signals**

Potential issues with analysis/interpretation of the assay

False positives

- BK polyoma virus (rare)
- Benign/reactive cells
  - Tapia *et al* Cancer Cytopathol. 2011 25;119(6):404-10
    - 27/77 (35.1%) benign with reactive changes were FISH+
- Tetraploidy
  - ? less specific predictor of malignancy
  - dividing cells, polyploidy in normal cells
    - ? >10 cells to define FISH+ result

Halling KC, Kipp BR. Adv Anat Pathol. 2008;15:279- 286

Bubendorf et al Am J Clin Pathol. 2001;116:79-86

Savic et al Int J Cancer. 2009;124:2899-2904

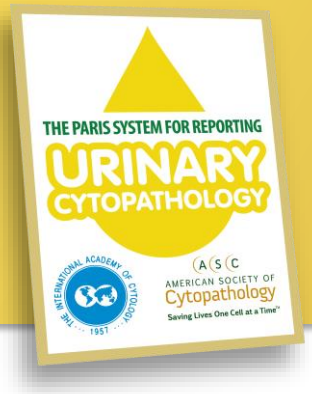
- **False negatives**
  - low-grade neoplasms
  - non-exfoliating - representative cells not shed into the urine sample
  - Lack of atypical cells on the slide used for FISH

Highlights importance of correlation with cytomorphology and clinical context

Potential of UroVysion FISH

Useful adjunctive test, improves sensitivity of urine cytology

- Does earlier detection translate into decreased mortality?
- Is negative predictive value sufficient to decrease the need for or frequency of cytoscopic follow-up?
- Is there a cost benefit - can/does incorporation of FISH results reduce no. of biopsies performed?



IV. Suspicious for HGUC

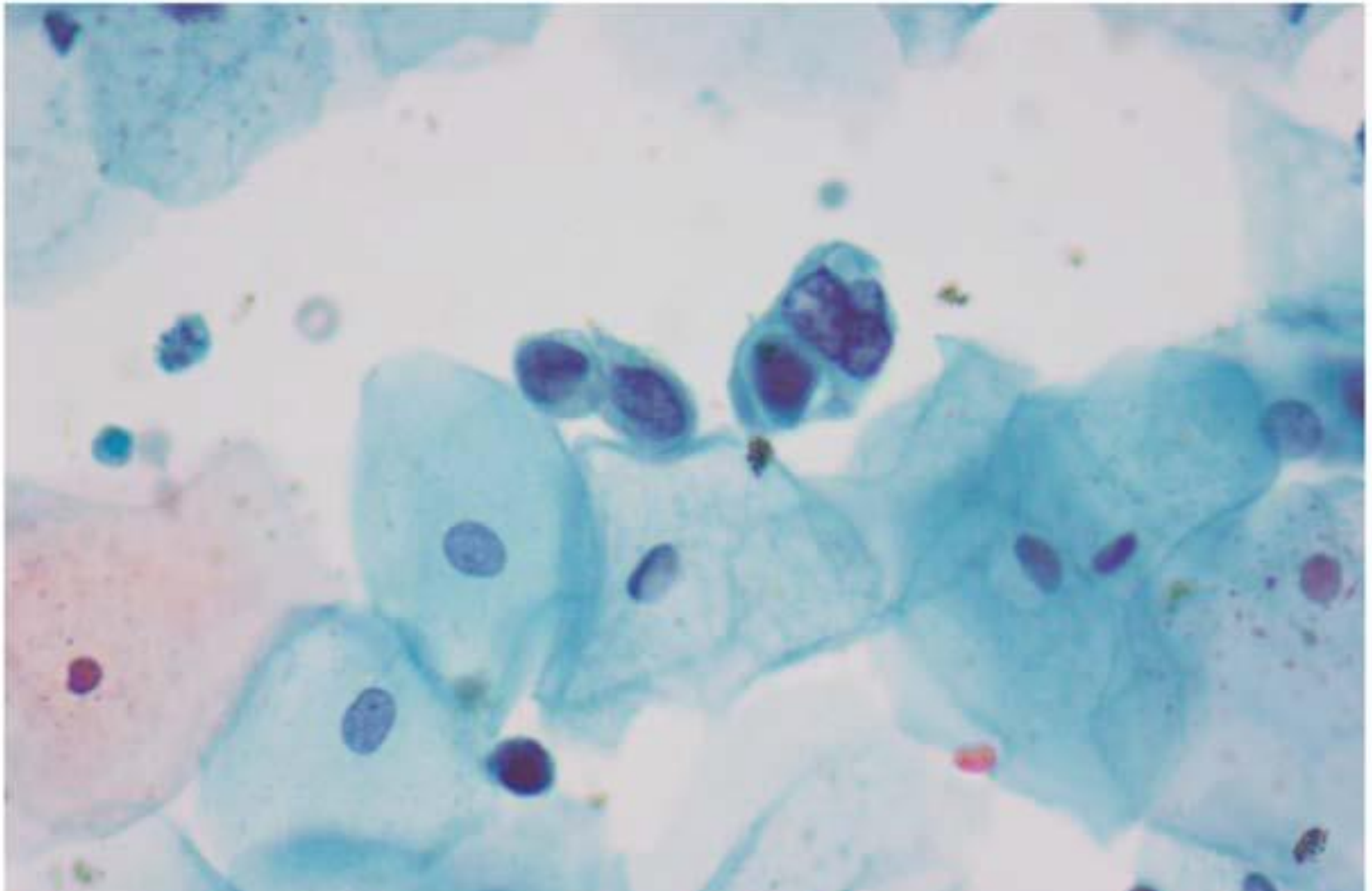
- Non-superficial and non-degenerated urothelial cells with a high **N/C ratio > 0.7 (required)**
- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus) **(required)**

and one of the following:

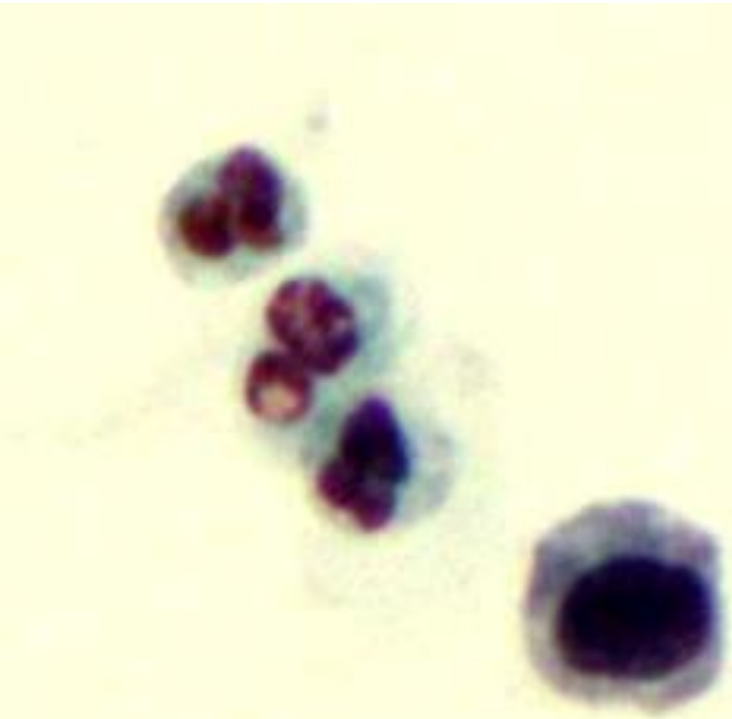
- **Irregular clumpy chromatin**
- **Irregular nuclear membranes**

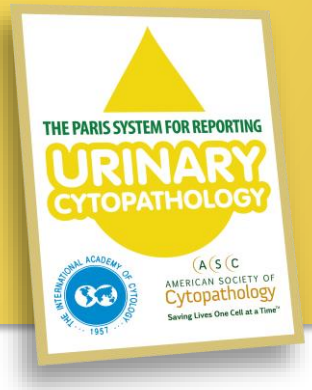
THE PARIS SYSTEM FOR REPORTING URINARY CYTOPATHOLOGY

Suspicious for HGUC



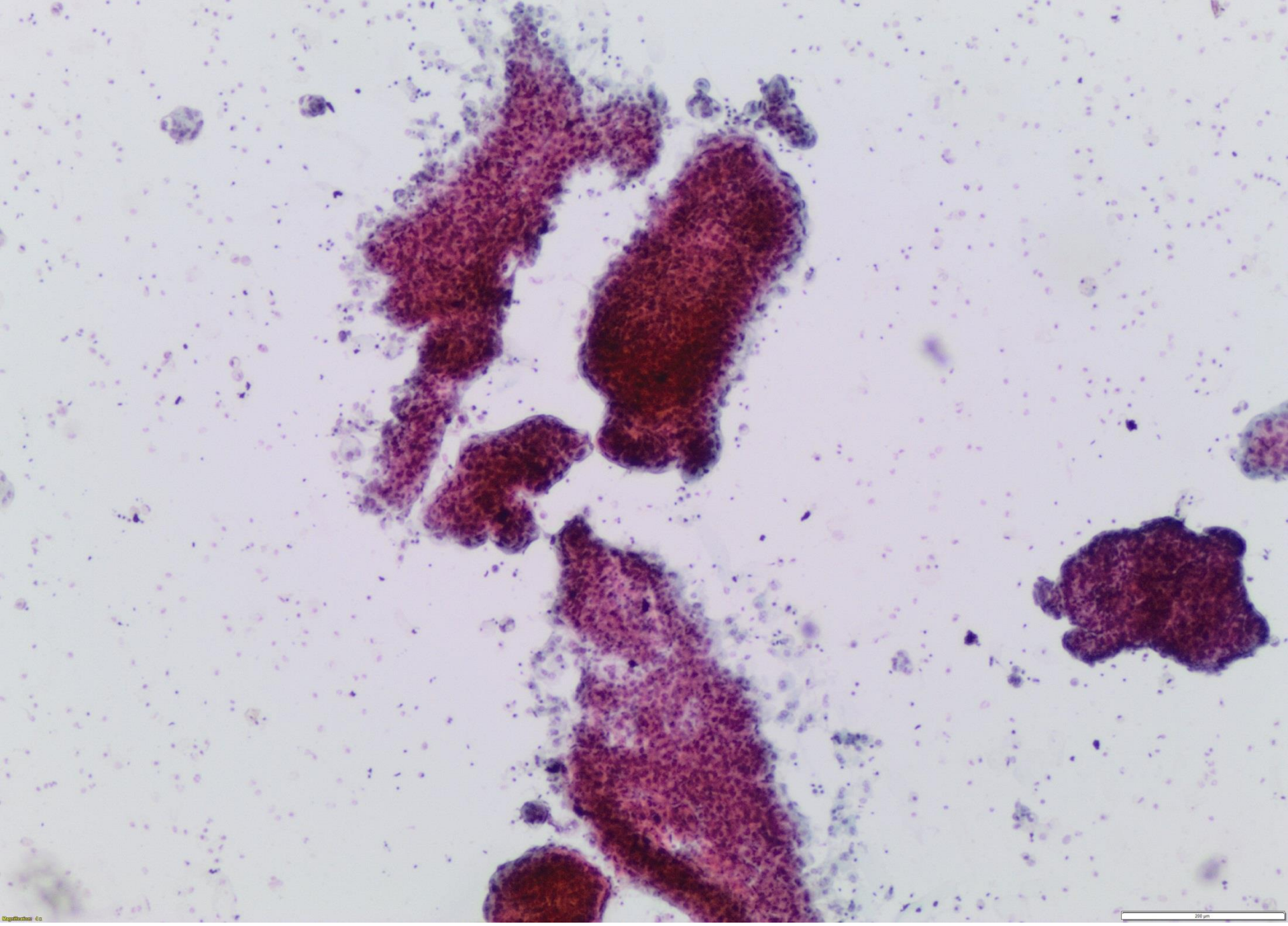
Suspicious for HGUC





V. Low grade urothelial neoplasm (LGUN)

- LGUN - combined cytologic term for low grade papillary urothelial neoplasms (LGPUN) (which include urothelial papilloma, PUNLMP and LGPUC) and flat, low grade intraurothelial neoplasia
- Three-dimensional cellular papillary clusters (defined as clusters of cells with nuclear overlapping, forming "papillae") with fibrovascular cores with capillaries (esp if cell block is examined)
- Diagnosis of LGUN may be made in correlation with cystoscopic or biopsy findings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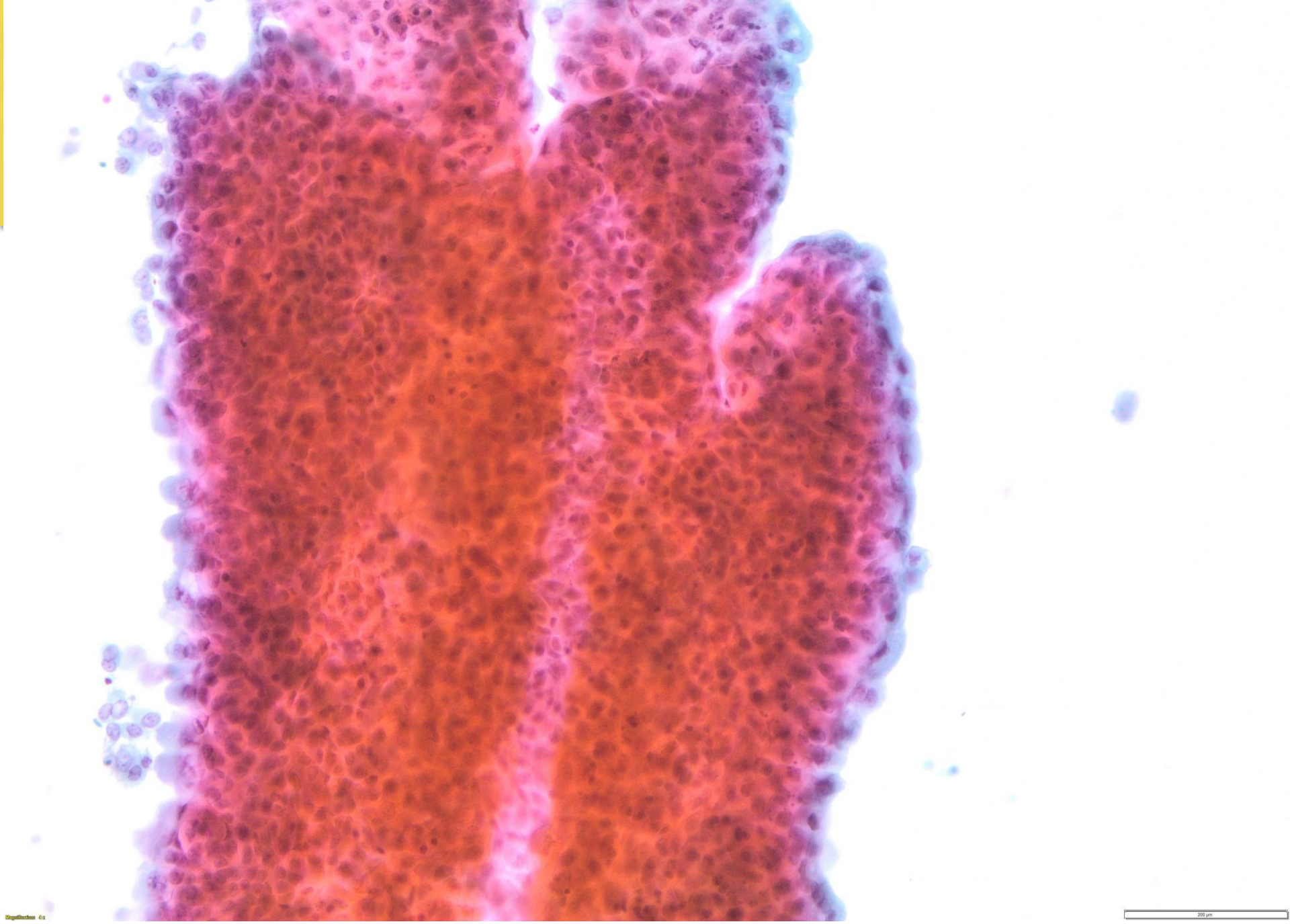
200 µm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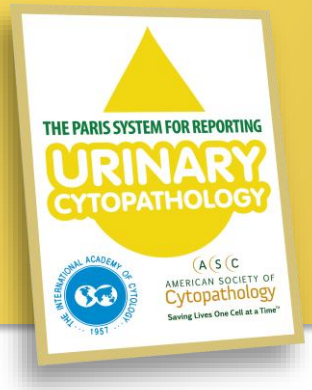
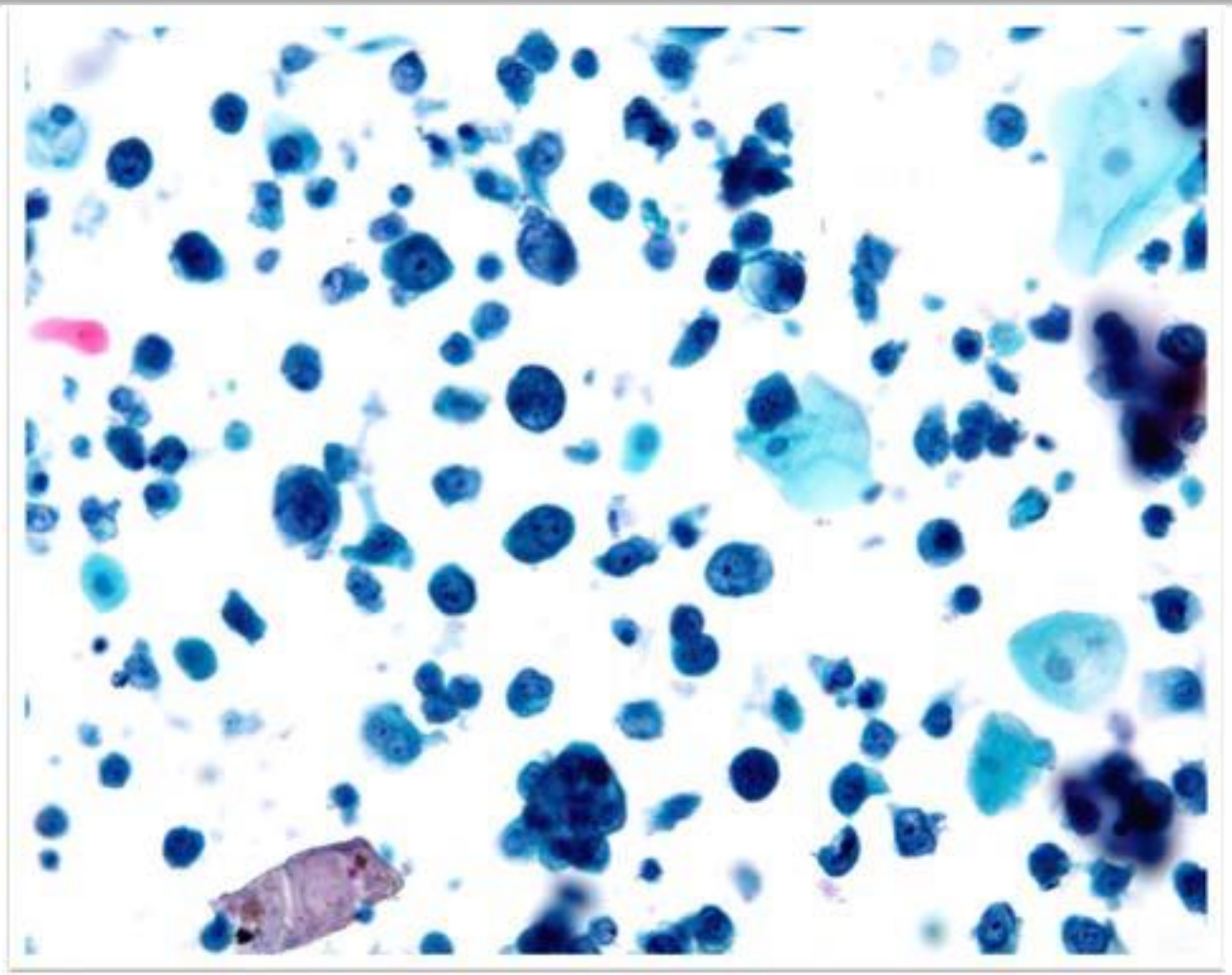


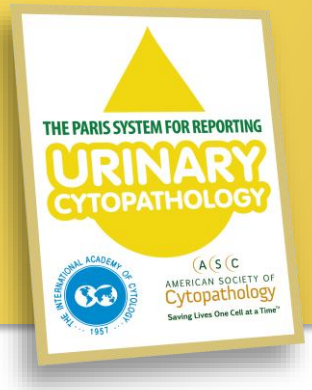
VI. High grade urothelial carcinoma (HGUC)

- "The number of atypical urothelial cells is an important criterion to classify urine cytology specimens into the 'positive' or the 'suspicious'/AUC-H categories. A cut off number of **>10 cells** to render a definitive diagnosis of HGUC seems valid from the clinical standpoint ."

Urine Cytology: Does the Number of Atypical Urothelial Cells Matter for distinguishing the "high-grade urothelial carcinoma" from the "suspicious for HGUC" cytological categories? (Brimo et al. USCAP 2015)

HGUC

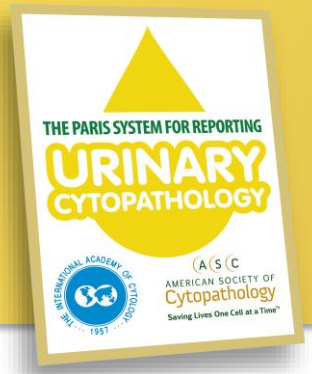




The Paris System: criteria for HGUC, Suspicious & Atypia*

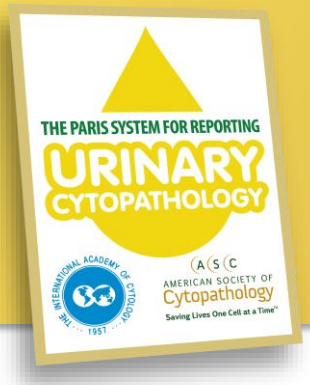
Category Criteria	HGUC	Suspicious for HGUC	Atypia
No. of atypical cells	>10	<10	<10
N:C ratio	>0.7	>0.7	0.5-0.7
Hyperchromasia	+	+	Any one of the three criteria
Clumped chromatin / Irregular nuclear borders	Either one of the two criteria	Either one of the two criteria	

***In conjunction with explanatory notes for each category**



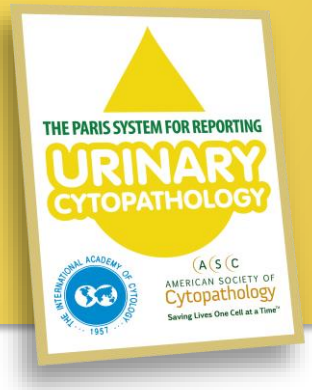
TPS categories: Risk of malignancy & clinical management

- Unsatisfactory/Non-diagnostic (?<5%) Repeat cytology, cystoscopy in 3 months if high clinical suspicion
- Negative for Malignancy (0-2%) Clinical follow up as needed
- Atypical Urothelial Cells (8-35%) . Clinical follow up as needed. Use of ancillary testing
- Suspicious for HGUC (50-90%). More aggressive follow up, cystoscopy, biopsy
- Low Grade Urothelial Neoplasm LGUN. (~10%). Need biopsy to further evaluate grade and stage
- High Grade UC (>90%). More aggressive follow up, cystoscopy, biopsy, staging
- Other malignancy (>90%). More aggressive follow up, cystoscopy, biopsy, staging



Further work

- The Paris system aims to standardize reporting of urinary tract cytology
- Published range of atypia 1.9% to 23.2% (suggested limit atypical and suspicious categories to <10%)
- Outcome data, reporting rates of categories, Atypia:HGUC ratio etc.
- Potential use of UroVysion FISH in Atypia cases



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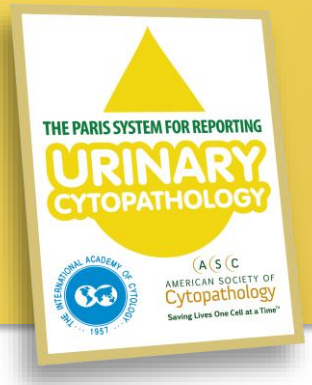
- Rosenthal DL, Vandenbussche CJ, Burroughs FH, Sathiyamoorthy S, Guan H, Owens C. The Johns Hopkins Hospital template for urologic cytology samples: part I-creating the template. Cancer Cytopathol. 2013 Jan;121(1):15-20.



References

- VandenBussche CJ, Sathiyamoorthy S, Owens CL, Burroughs FH, Rosenthal DL, Guan H. The Johns Hopkins Hospital template for urologic cytology samples: parts II and III: improving the predictability of indeterminate results in urinary cytologic samples: an outcomes and cytomorphologic study. Cancer Cytopathol. 2013 Jan;121(1):21-8.

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