ThinPrep® Non-Gyn Lecture Series

Urinary Cytology

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Benefits of ThinPrep® Technology

The use of ThinPrep Non-Gyn for specimens from the urinary tract:

- Optimizes cell preservation
- Standardizes specimen preparation
- Simplifies slide screening
- Offers the versatility to perform ancillary testing

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

ThinPrep® Non-Gyn

Materials

- ThinPrep® 2000 Processor or ThinPrep® 5000 Processor
- ThinPrep Microscope Slides (Non-Gyn)
- ThinPrep UroCyte® Microscope Slides
- ThinPrep Non-Gyn Filters (Blue)
- ThinPrep UroCyte Filters (Yellow)
- Multi-Mix™ Racked Vortex
- CytoLyt® and PreservCyt® Solutions
- Optional - UroCyte® Urine Collection Kit

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ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

Materials

- 50 mL capacity "swing arm" centrifuge
- 50 mL centrifuge tubes
- Slide staining system and reagents
- 1 mL plastic transfer pipettes
- 95% alcohol
- Coverslips and mounting media
- Optional - glacial acetic acid and saline for troubleshooting

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

ThinPrep® Non-Gyn

Hologic® Solutions

- CytoLyt® Solution
- PreservCyt® Solution

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MAN-01322-4750 Rev. 002, CytoLyt IFU for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.
MAN-01320-4750 Rev. 005, NonGYN PreservCyt IFU for US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.

- Methanol-based, buffered preservative solution
- Lyses red blood cells
- Prevents protein precipitation
- Dissolves mucus
- Cells are preserved for 8 days at room temperature
- Intended as transport medium
- Used in specimen preparation prior to processing

MAN-01322-4750 Rev. 002, CytoLyt IFU for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.

ThinPrep® Non-Gyn

Hologic® Solutions
PreservCyt® Solution

- Methanol-based, buffered preservative solution designed to support cells during transport and processing
- Specimens must be stored in PreservCyt Solution prior to processing
- PreservCyt Solution cannot be substituted with any other reagents
- Cells in PreservCyt Solution are preserved for up to 3 weeks in a temperature range of 4°-37°C

MAN-01320-4750 Rev. 005, NonGYN PreservCyt IFU for US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.

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Hologic® Supplies

UroCyte® Collection Kit, Filters and Slides

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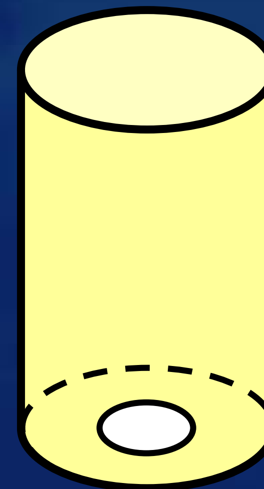
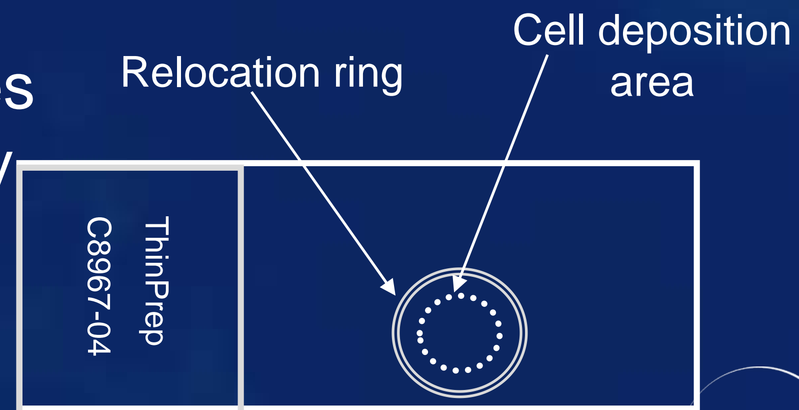
MAN-01324-4750 Rev 002 UroCyte PreservCyt IFU in the UroCyte vial kit for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.
MAN-01323-4750 Rev 002 UroCyte PreservCyt IFU in the UroCyte urine collection kit for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc; 2019

Hologic® Supplies UroCyte® Filters and Slides

- ThinPrep® 2000 processor compatible with software card
- ThinPrep 5000 processor run on Sequence UroCyte
- Specialized filter: 10 mm diameter filter area, 8.5 micron pore size
- Specialized microscope slides
- 16 mm diameter ring for easy cell spot location





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Sample Collection

- Routine Urine Collection:
  - Fresh – recommended
  - CytoLyt® Solution
    - If fresh collection is not possible, collect samples directly into CytoLyt Solution
    - The minimum CytoLyt to sample ratio should be 1:3 and is not considered a wash step, but only a collection step
  - PreservCyt® Solution
    - Fresh urine can be mixed with a 2:1 urine-to-PreservCyt Solution ratio

MAN-01322-4750 Rev. 002, CytoLyt IFU for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.
MAN-01320-4750 Rev. 005, NonGYN PreservCyt IFU for US, Canada, and Europe, Marlborough, MA: Hologic, Inc.; 2019.
ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Collection

- UroCyte® Collection
  - ThinPrep® UroCyte Urine collection kit – recommended or process fresh urine

Note: Fresh urine can be mixed with a 2:1 urine-to-PreservCyt® Solution ratio and stored for up to 48 hours before processing.

Note - If using the UroCyte Urine Collection Kit, do not exceed a 2:1 ratio of urine to PreservCyt Solution. If the urine volume exceeds 60 mL, pour off excess. A minimum volume of 33 mL of urine is required to perform the UroVysion™ assay.

MAN-01323-4750 Rev 002 UroCyte PreservCyt IFU in the UroCyte urine collection kit for the US, Canada, and Europe, Marlborough, MA: Hologic, Inc; 2019
ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Overview Routine Urine Cytology

1. Sample collection
2. Concentrate by centrifugation
3. Pour off supernatant and vortex to resuspend cell pellet
4. Add 30 mL of CytoLyt® Solution. Repeat centrifugation, pour off supernatant and vortex to resuspend cell pellet
5. Evaluate cell pellet. If cell pellet is not free of blood, repeat from step 4
6. Add recommended # of drops of specimen to PreservCyt® Solution Vial
7. Allow to stand in PreservCyt Solution for 15 minutes
8. Prepare slide on ThinPrep® 2000 processor using Sequence 2 (FLU/FNA) or ThinPrep® 5000 processor using Sequence Non-Gyn
9. Fix, Stain, and Evaluate

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Overview UroCyte®

1. Sample collection.
2. Transfer the sample evenly into two labeled 50 mL centrifuge tubes, concentrate by centrifugation.
3. Pour off supernatant and vortex to resuspend cell pellet.
4. Add 30 mL of CytoLyt® Solution to one 50 mL tube and vortex. Transfer the contents of this tube into the second 50 mL tube and vortex. The specimen is now combined into one 50 mL tube. The empty tube can be discarded. Centrifuge, pour off supernatant and vortex to resuspend cell pellet.
5. Evaluate cell pellet appearance. If pellet is not free of blood, add 30 mL of CytoLyt Solution and repeat from step 4.
6. Add entire specimen to PreservCyt® Solution Vial and allow to stand in PreservCyt Solution for 15 minutes.
7. Prepare slide on ThinPrep® 2000 processor using Sequence 5 (UroCyte) or ThinPrep 5000 processor using Sequence UroCyte.
8. Fix, stain, and evaluate cytology OR perform molecular diagnostic testing according to manufacturer's instructions for use.

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Centrifugation 600*g* for 10 minutes or 1200*g* for 5 minutes

  - Concentrate cellular material in order to separate the cellular components from the supernatant

  Refer to Centrifuge Speed Chart in the ThinPrep® 2000 or ThinPrep 5000 Owners Manual, Non-Gynecologic section to determine the correct speed for your centrifuge to obtain

  force of 600*g* or 1200*g*.

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Pour off supernatant
  - Invert the centrifuge tube 180° in *one smooth movement*, pour off all supernatant and return tube to its original position

Note: Failure to completely pour off the supernatant may result in a sparsely cellular sample (due to dilution of the cell pellet).

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Vortex to re-suspend cell pellet
  - Purpose of this step is to randomize the cell pellet and to improve the results of the subsequent CytoLyt® solution washing procedure
  - Place the centrifuge tube onto a vortexor and agitate the cell pellet for 3 seconds or vortex manually by syringing the pellet back and forth with a plastic pipette

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- CytoLyt® Solution Wash
  - Preserve cellular morphology while lysing red blood cells, dissolving mucus and reducing protein precipitation
  - Add 30 mL of CytoLyt Solution to a cell pellet, concentrate by centrifugation, pour off the supernatant, vortex and evaluate cell pellet

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Evaluate cell pellet
  - If cell pellet is white, pale pink, tan or not visible. Calculate number of drops of specimen to be added to the PreservCyt® Solution Vial *(will be discussed in detail on future slides)*
  - If cell pellet is distinctly red or brown indicating the presence of remaining blood conduct a second CytoLyt® Wash

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Calculate how many drops of specimen to add to PreservCyt® vial:
  - If pellet volume is > 1 mL *(if not consider next 2 slides)*
    - Add 1 mL of CytoLyt® Solution into the tube and vortex briefly to resuspend the cell pellet
    - Transfer 1 drop of the specimen to a fresh PreservCyt Solution Vial

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Calculate how many drops of specimen to add to PreservCyt® vial:
  - If pellet is clearly visible and pellet volume is < 1 mL *(if not consider next slide)*
    - Vortex pellet and transfer 2 drops to a fresh PreservCyt solution vial

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Sample Preparation Techniques

- Calculate how many drops of specimen to add to PreservCyt® vial:
  - If pellet is not visible or scant,
    - Add contents of a fresh PreservCyt Solution Vial into the tube and vortex briefly to mix the solution
    - Pour entire sample back into the vial

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting Sample Preparation

- Due to the biological variability among samples and variability in collection methods, standard processes may not always yield a satisfactory and uniformly distributed preparation on the first slide.

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

Troubleshooting Sample Preparation

- After staining, you may observe the following irregularities:
  - Non-uniform distribution of cells in the cell spot *without* a “sample is dilute” message
  - Uneven distribution in the form of a ring or halo of cellular material and/or white blood cells
  - A sparse cell spot lacking in cellular component and containing blood, protein and debris – may be accompanied by a “sample is dilute” message

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Techniques Used in Troubleshooting

- Diluting the Sample 20 to 1
- Glacial Acetic Acid Wash for Blood and Non-Cellular Debris
- Saline Wash for Protein

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Techniques Used in Troubleshooting

- Diluting the sample 20 to 1
  - Add 1 mL of the sample that is suspended in PreservCyt® solution to a new PreservCyt solution vial (20 mL). This is most accurately done with a calibrated pipette

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Techniques Used in Troubleshooting

- Glacial acetic acid wash for blood and non-cellular debris
  - If sample is bloody, it can be further washed using a solution of 9 parts CytoLyt® solution and 1 part glacial acetic acid

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

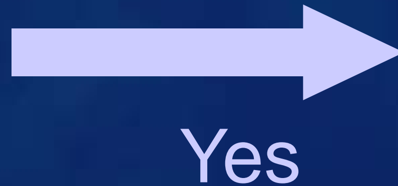
Techniques Used in Troubleshooting

- Saline wash for protein
  - If sample contains protein, it can be further washed with saline solution in place of CytoLyt® solution

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

Troubleshooting
Bloody or Proteinaceous Specimens

"Sample is Dilute" message



Yes

Check to see if cellularity is adequate. If not, use more of the pellet, if available and prepare new slide.

No, continue to next slide.

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting
Bloody or Proteinaceous Specimens

Does the slide have a "halo" of cellular material and/or white blood cells?

Yes

Dilute 20:1 by adding 1 mL of residual sample to a new PreservCyt® solution vial and prepare new slide.

If halo is present on the new slide, contact Hologic® Technical Service.

No, continue to next slide.

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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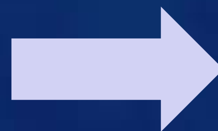
Troubleshooting Bloody or Proteinaceous Specimens

Is the slide sparse and does it contain blood, protein or non-cellular debris?



Yes-blood or non-cellular debris

Centrifuge remaining specimen from PreservCyt® vial, pour off and vortex. Add 30 mL of a 9:1 CytoLyt® to glacial acetic acid solution to the sample, centrifuge, pour off and vortex. Add appropriate number of drops to PreservCyt vial and prepare new slide. *If the resulting slide is sparse, contact Hologic Technical Service.*

No

Yes-protein

Centrifuge remaining specimen from PreservCyt vial, pour off and vortex. Add 30 mL of saline to sample, centrifuge, pour off and vortex. Add appropriate number of drops to PreservCyt vial and prepare new slide. *If resulting slide is sparse, contact Hologic Technical Service.*

Contact Hologic® Technical Service

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

Troubleshooting Common Artifacts

- Smudged nuclear detail
- Compression artifact
- Staining artifact
- Edge of the cylinder artifact

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting Common Artifacts

- Smudged nuclear detail
  - May occur if specimen is collected in saline, PBS or RPMI
  - To avoid this, collect either fresh, or in CytoLyt® or in PreservCyt® solution

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting Common Artifacts

- Compression Artifact
  - Appears as “air-dry” artifact on the perimeter of the cell spot
  - Due to a compression of cells between the edge of the filter and the glass slide

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ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting Common Artifacts

- Staining Artifact
  - Mimics air drying
  - Appears as a red or orange central staining primarily in cells clusters or groups
  - Due to the incomplete rinsing of the counter stains
  - To eliminate this artifact, fresh alcohol baths or an additional rinse step after the cytoplasmic stains is required

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Troubleshooting Common Artifacts

- Edge of the Cylinder Artifact
  - Narrow rim of cellular material just beyond the circumference of the cell spot
  - Results from cells from the outer edge of the wet filter cylinder being transferred to the glass slide

ThinPrep 2000 Processor [operator's manual]. MAN-02585-001. Marlborough, MA: Hologic, Inc.; 2018.
ThinPrep 5000 Processor [operator's manual]. MAN-02203-001. Marlborough, MA: Hologic, Inc.; 2018.

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Specimen Types

- Voided Urine
- Catheterized Bladder Urine
- Cystoscopy specimens:
    a. Bladder Urine
    b. Bladder Wash
    c. Ureter or Renal Wash
- Ileal Conduit Urine
- Retrograde Brushing

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Voided Urine

- Easily obtained[2]
- Often contaminated with cells from the perineum or the genital tract[2]
- Samples entire urinary tract[2]
- Cytology remains one of the best ways to diagnose a variety of bladder lesions, most importantly HGUC[1]
- Cells can show degeneration[1,2]
- Low numbers of urothelial cells may be present[2]

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1. Cibas ES, Ducatman BS. Urine and Bladder Washings - Ancillary Techniques. In: *Cytology - Diagnostic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2009:123-124.
2. DeMay RM. Urine. In: *The Art & Science of Cytopathology*. 2nd ed. Chicago, IL: American Society for Clinical Pathology; 2012:435-488.

Catheterized Urine

- May see instrumentation effect (lithiasis) and/or lubricant material[1]
- Lesions in the urethra may be missed[2]
- Invasive, uncomfortable and risk of urinary tract infection to the patient[1,2]
- If catheter is indwelling cellular degeneration can be pronounced due to possible extended length of time at room temperature[1]
- Urothelial cell clusters may be scraped off by the tip of the catheter, mimicking the appearance of a low-grade papillary neoplasm[1]

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1. Cibas ES, Ducatman BS. Urine and Bladder Washings - Ancillary Techniques. In: *Cytology - Diagnostic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2009:123-124.
2. DeMay RM. Urine. In: *The Art & Science of Cytopathology*. 2nd ed. Chicago, IL: American Society for Clinical Pathology; 2012:435-488.

Bladder Urine & Washing

- Bladder urine is collected using a catheter followed by an irrigation of sterile isotonic saline
  - Diagnostic sensitivity is enhanced if both the washing and the urine present in the bladder at cystoscopy are submitted for evaluation
- Used to diagnose and monitor urothelial neoplasia
- Highly cellular specimens containing well preserved cells
- Method of choice when bladder malignancy is suspected
- Almost no extraneous cellular contamination with excellent preservation if processed quickly, however, contamination from lubricant can render specimens unsatisfactory
- Does not sample the upper urinary tract
- Risks include infection, spread of tumor and limited sample area
- Large clusters of urothelial cells (deep and superficial), large multi-nucleated umbrella cells, squamous cells and rare red blood cells are common expected findings

DeMay RM. Urine. In: *The Art & Science of Cytopathology*. 2nd ed. Chicago, IL: American Society for Clinical Pathology; 2012:435-488.

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Retrograde Catheterization with Washings or Brushings

- Sampling and diagnosis of upper urinary tumors can be achieved using this method
- Able to sample inaccessible sites with the ureteropyeloscope and take direct sampling.
- Specimens are similar to those collected from the bladder
  - Urothelial cells from the upper urinary tract have a more atypical appearance than from the lower urinary tract
  - Often see tight pseudopapillary clusters, due to instrumentation or lithiasis

DeMay RM. Urine. In: *The Art & Science of Cytopathology*. 2nd ed. Chicago, IL: American Society for Clinical Pathology; 2012:435-488.

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Ileal Conduit/Loop Urine

- During a cystectomy, a portion of the bowel is used as a urine conduit[1,2]
- Commonly contains:
  - Abundant, intestinal glandular epithelial cells[1,2]
    - Mostly seen as single, very degenerated cells resembling macrophages[1,2]
  - Urothelial cells are sparse or absent[2]
- Important to screen thoroughly as patients with a history of bladder cancer are at increased risk for developing tumors of the ureters and kidneys[1]

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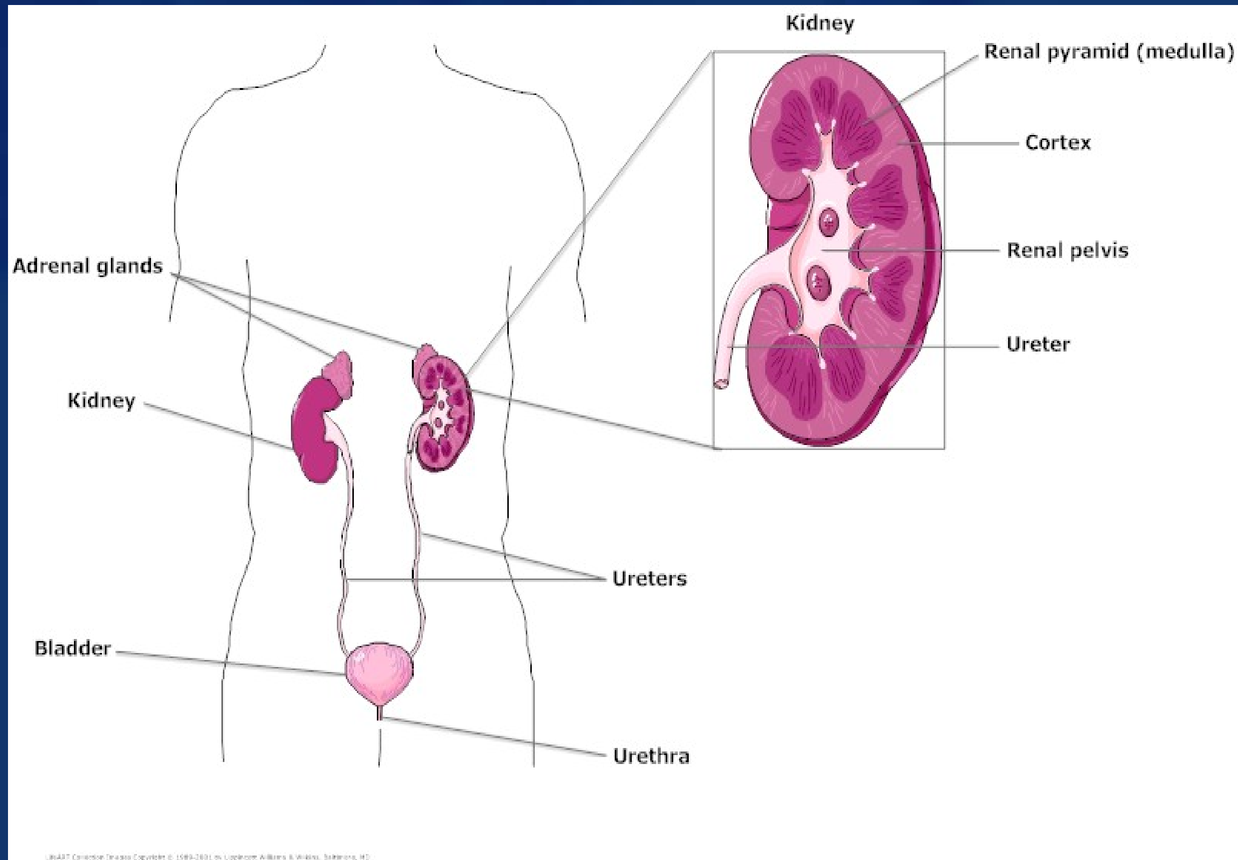
1. Cibas ES, Ducatman BS. Urine and Bladder Washings - Ancillary Techniques. In: *Cytology - Diagnostic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2009:123-124.
2. DeMay RM. Urine. In: *The Art & Science of Cytopathology*. 2nd ed. Chicago, IL: American Society for Clinical Pathology; 2012:435-488.

Urinary Tract Anatomy



SmartDraw® (Standard Edition) [Software]. (2011). Retrieved from http://www.smartdraw.com

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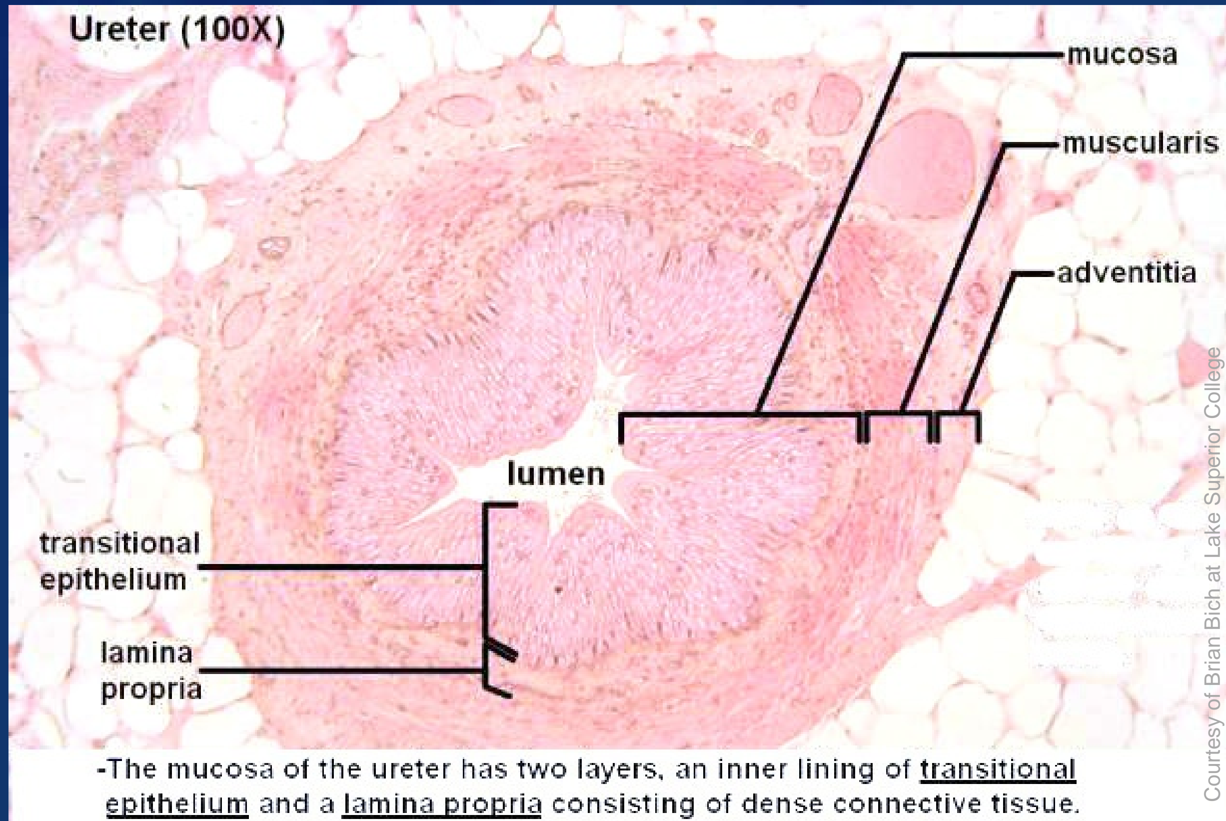
Histology of Epithelium
Ureter



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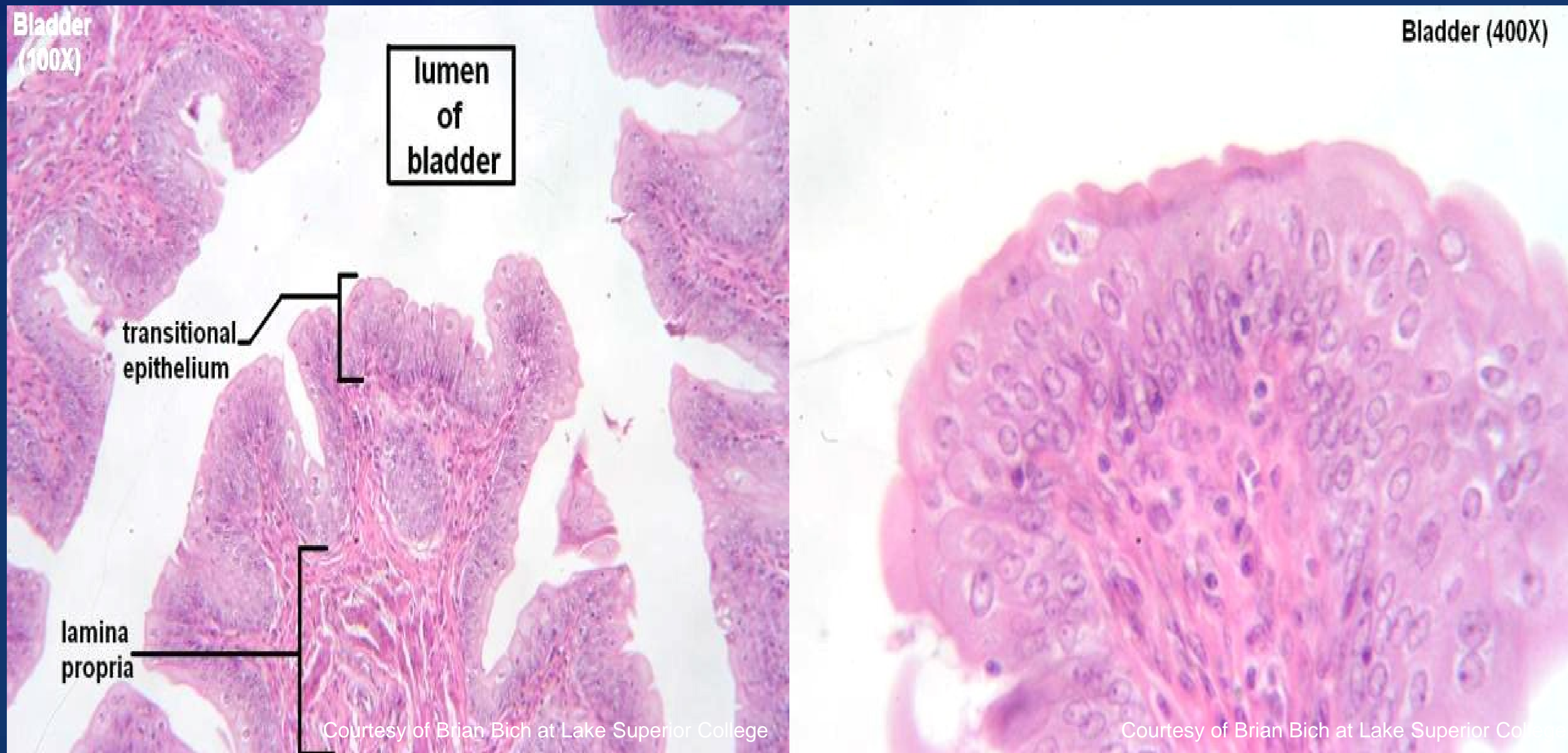
Bich, Brian. *Ureter, Bladder . 2008. Photograph.* Lake Superior College, Duluth, MN. Web. *Lake Superior College.* [http://employee.lsc.edu/faculty/BrianBich/Picture%20Library/Form AllItems.aspx?RootFolder=%2Ffaculty%2FBrianBich%2FPicture%20Library%2FAnat%2DPhys%20II%20%28Biol%201141%29&View={997D7559-348B-48F0-A9FE-07741C9C8B65}

Histology of Epithelium
Bladder



Bich, Brian. *Ureter, Bladder . 2008. Photograph.* Lake Superior College, Duluth, MN. Web. *Lake Superior College.* [http://employee.lsc.edu/faculty/BrianBich/Picture%20Library/Form AllItems.aspx?RootFolder=%2Ffaculty%2FBrianBich%2FPicture%20Library%2FAnat%2DPhys%20II%20%28Biol%201141%29&View={997D7559-348B-48F0-A9FE-07741C9C8B65}

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Biological Nature of Urine

- Waste product of metabolism, made in the kidneys and is formed by filtration, reabsorption, and tubular secretion
- Chiefly comprised of water (91 to 96%) but also contains inorganic salts, protein, hormones and other metabolites
- Specific gravity range of 1.003 to 1.035
- pH range of 5.5 to 7.0

Biology Online Dictionary. Urine. https://www.biology-online.org/dictionary/Urine. Accessed June 3, 2019.

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- Benign urothelial cells
  - Cytoplasm is abundant and may be foamy to dense
  - Chromatin is finely granular and nucleoli may be present with multinucleation (umbrella cells)

ThinPrep Non-GYN Morphology Reference Atlas: Urinary 119-147

ThinPrep® Non-Gyn

40x

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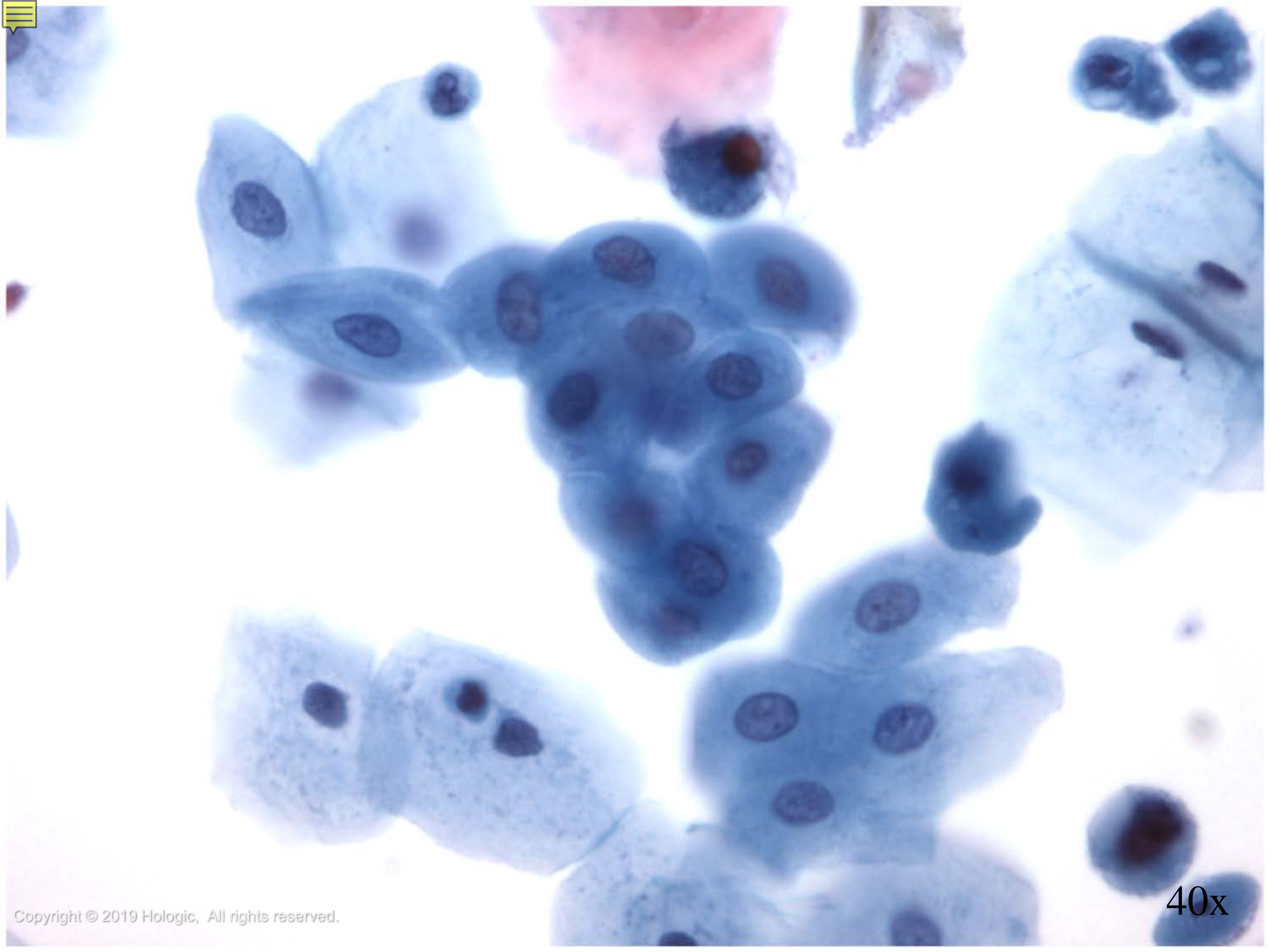

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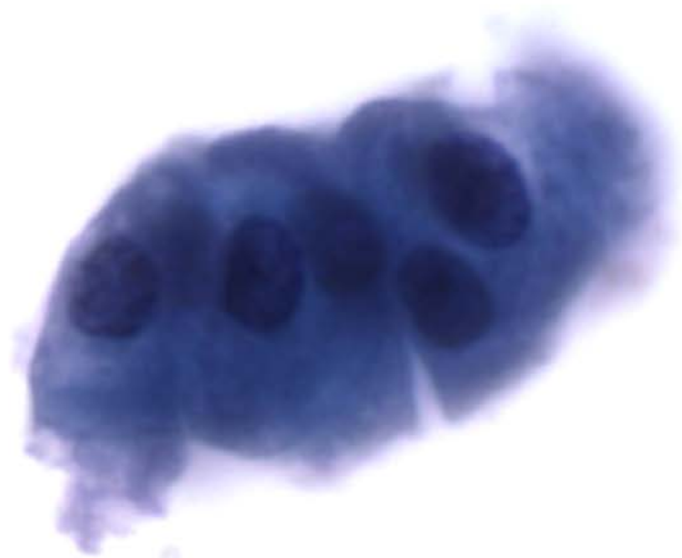

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Normal Components and Findings

- Benign squamous and glandular cells
  - Benign squamous cells may be shed from the trigone or be present as contaminant
  - Glandular cells may be shed from many sites including the paraurethral and prostate glands and found in loop urines

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Normal Components and Findings

- Crystals
- Contaminants
  - Bacteria and yeast
  - Pollen and talc
  - Spermatozoa and seminal vesicle cells
  - Lubricant
  - Corpora amylacea

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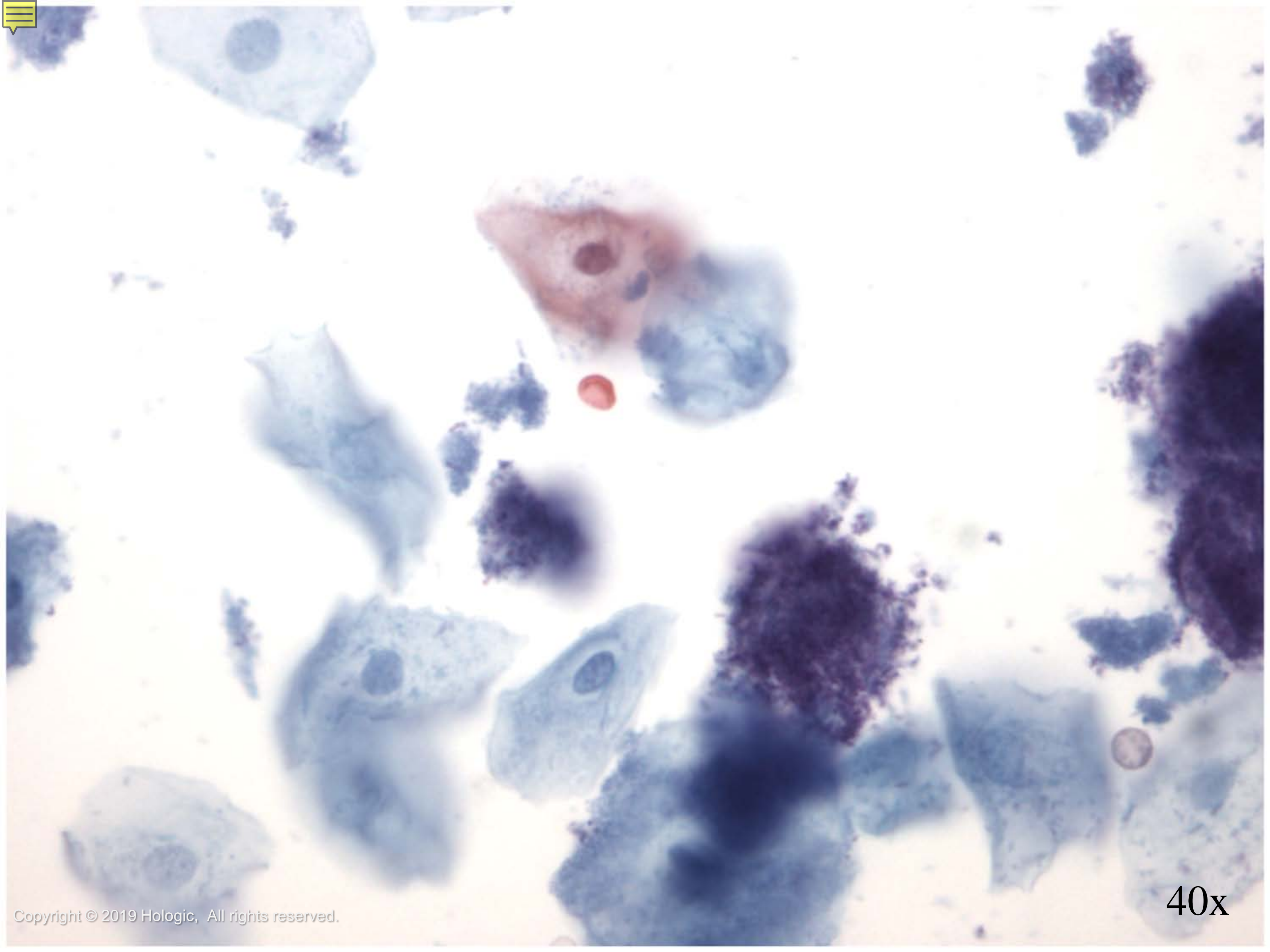

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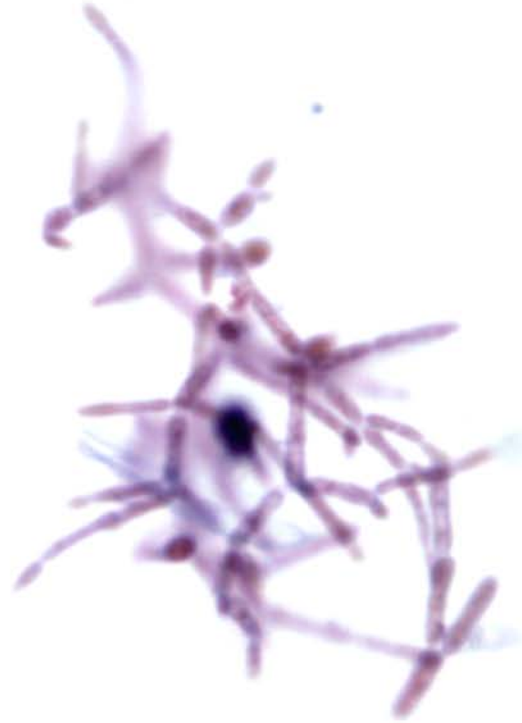

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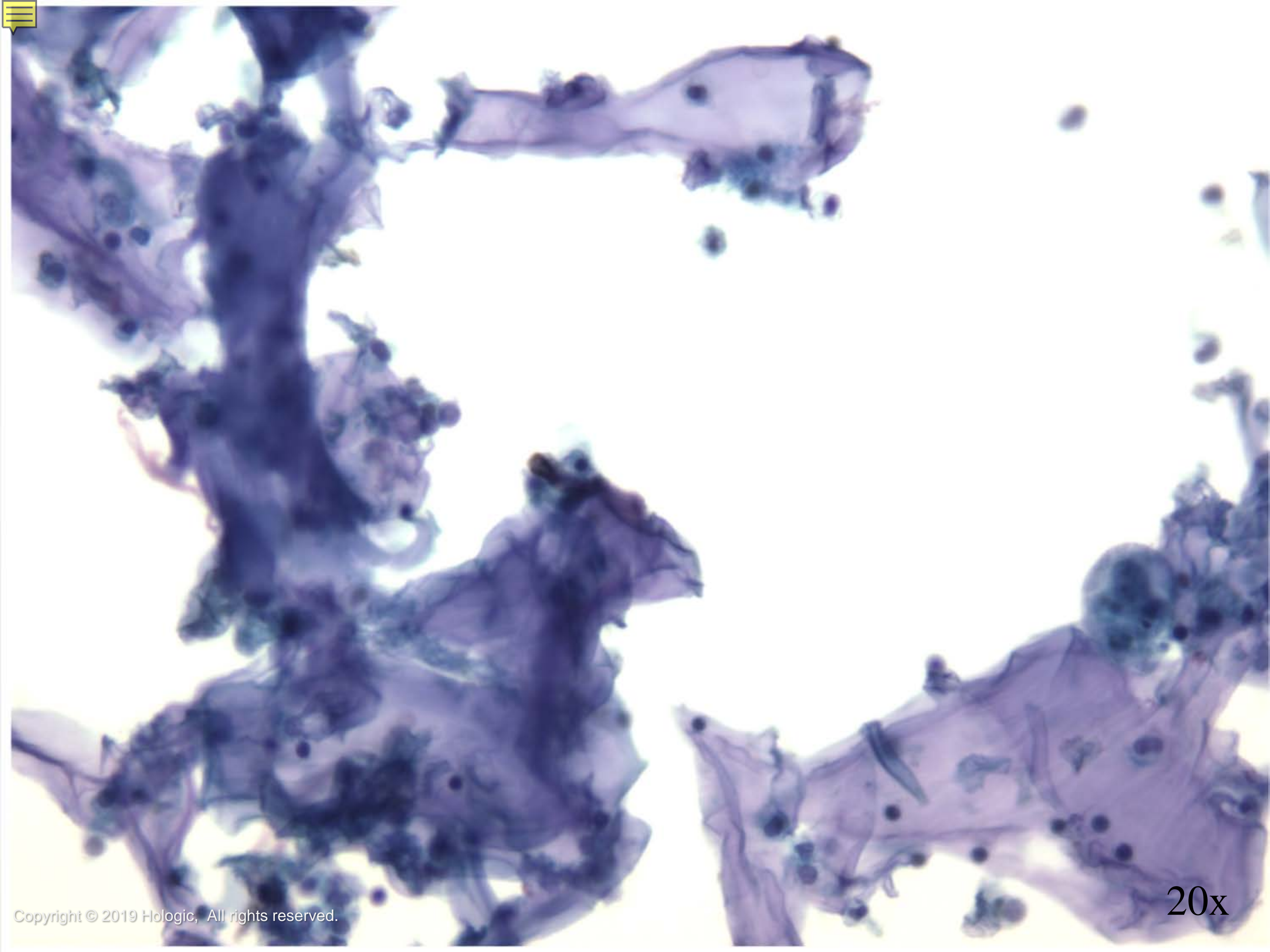

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Other Disease Findings

Renal Tubular Cells

- Small columnar cells occurring singly, in small sheets or as a granular cast.
- Their presence is associated with kidney disease.

Casts

- Their presence may be associated with kidney disease, infection and/or bleeding in the kidney.
- May be filled with RBCs, WBCs, degenerated renal tubular cells (granular) or amorphous, eosinophilic proteinaceous material (hyaline)

Inflammation and RBCs

- May represent trauma, infection or tumor. Eosinophils may be associated with drug induced interstitial cystitis.

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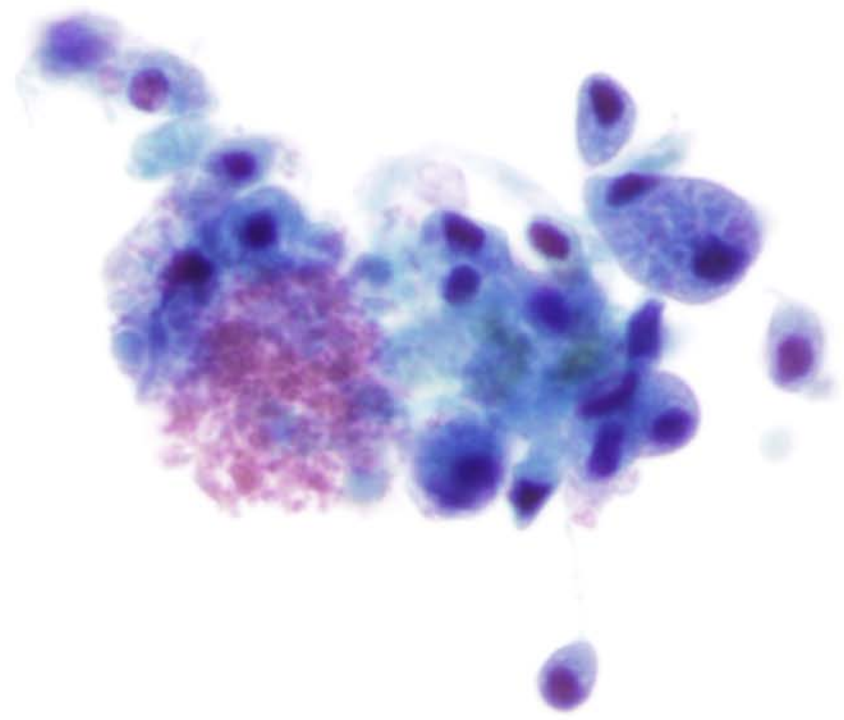

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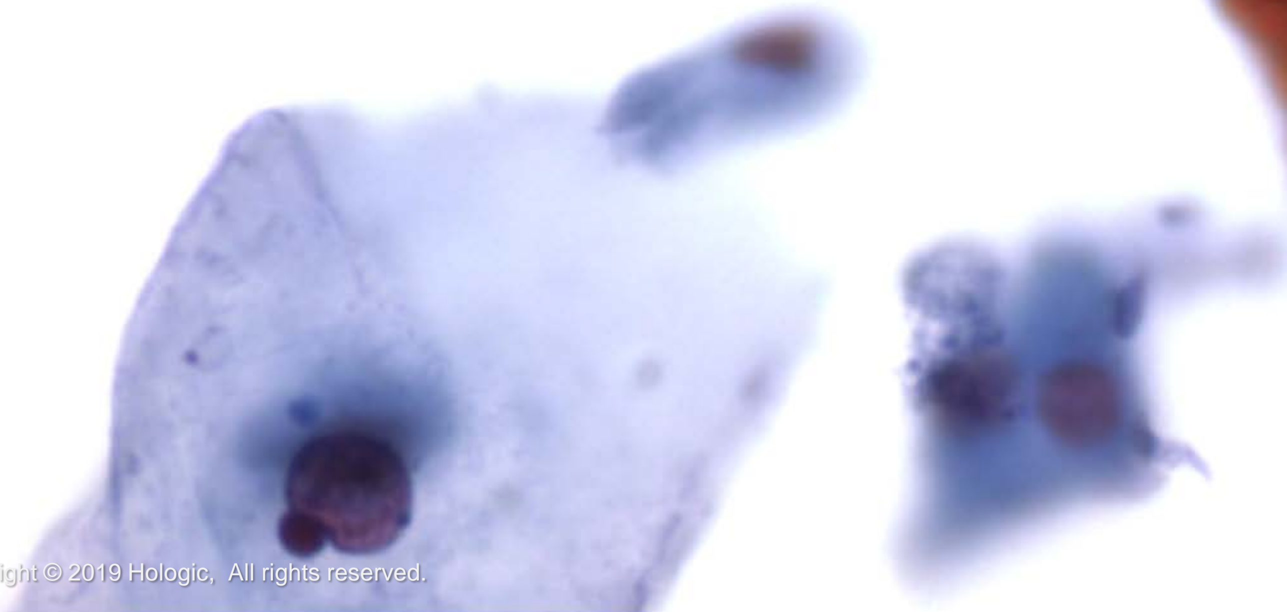

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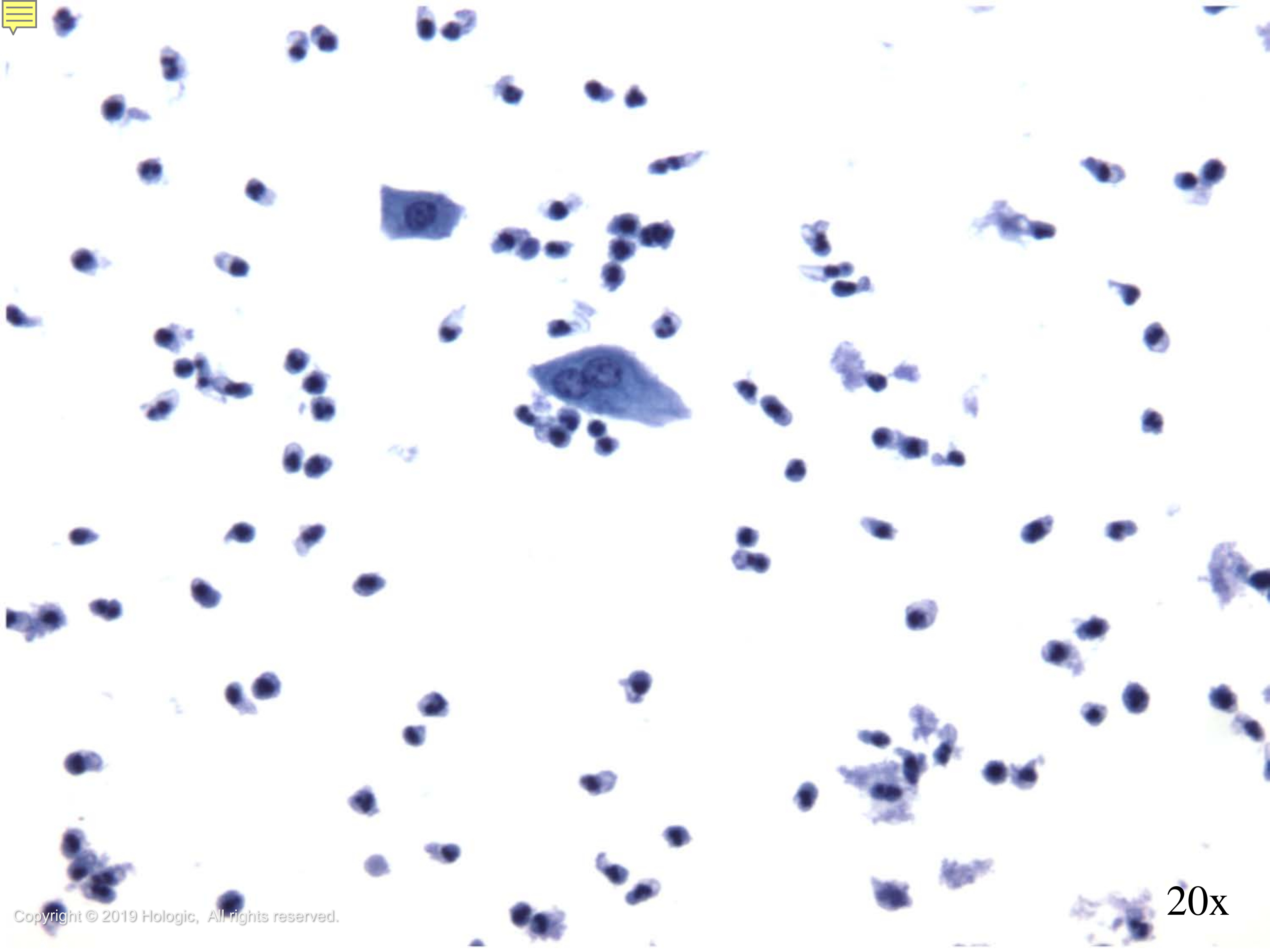

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Benign Entities and Changes

- Reactive changes are very common findings in urinary cytology and may be due to:
  - Instrumentation
  - Infection/Inflammation
  - Drug therapy
  - Calculi

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Reactive Changes

- Features of reactive urothelial cells may include:
  - Marked cellular and nuclear enlargement
  - Prominent nucleoli
  - Coarser chromatin pattern
  - Multinucleation
  - Abundant cytoplasm remains
  - Large honeycombed sheets (especially with instrumentation)

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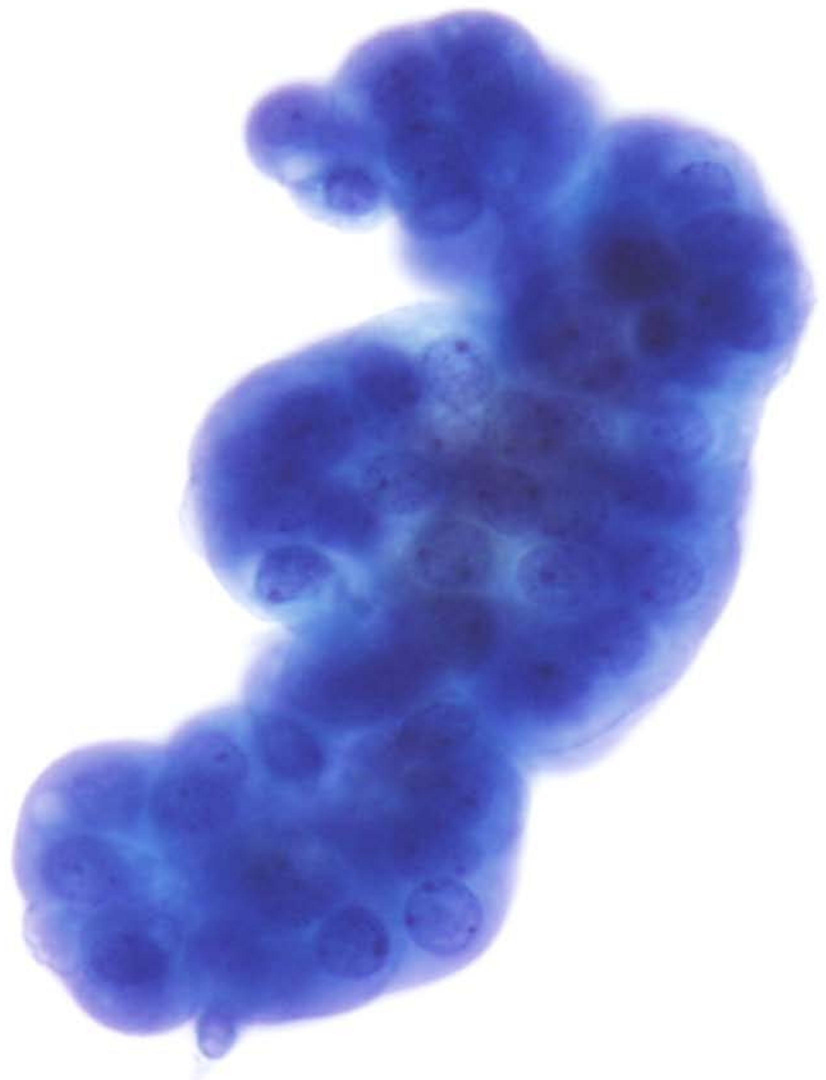

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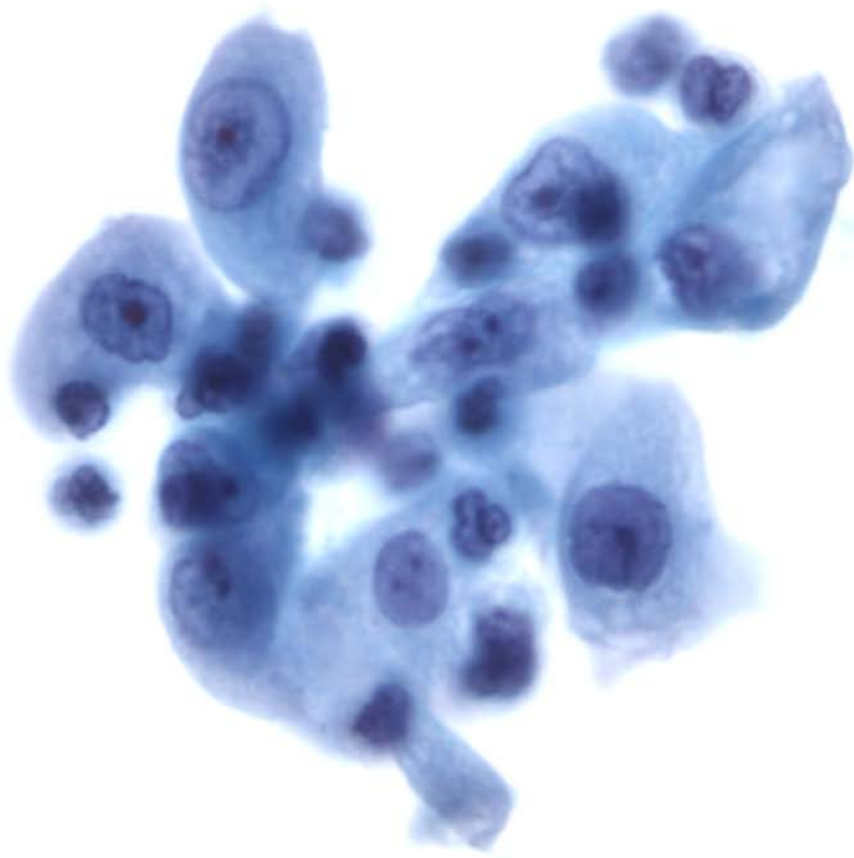

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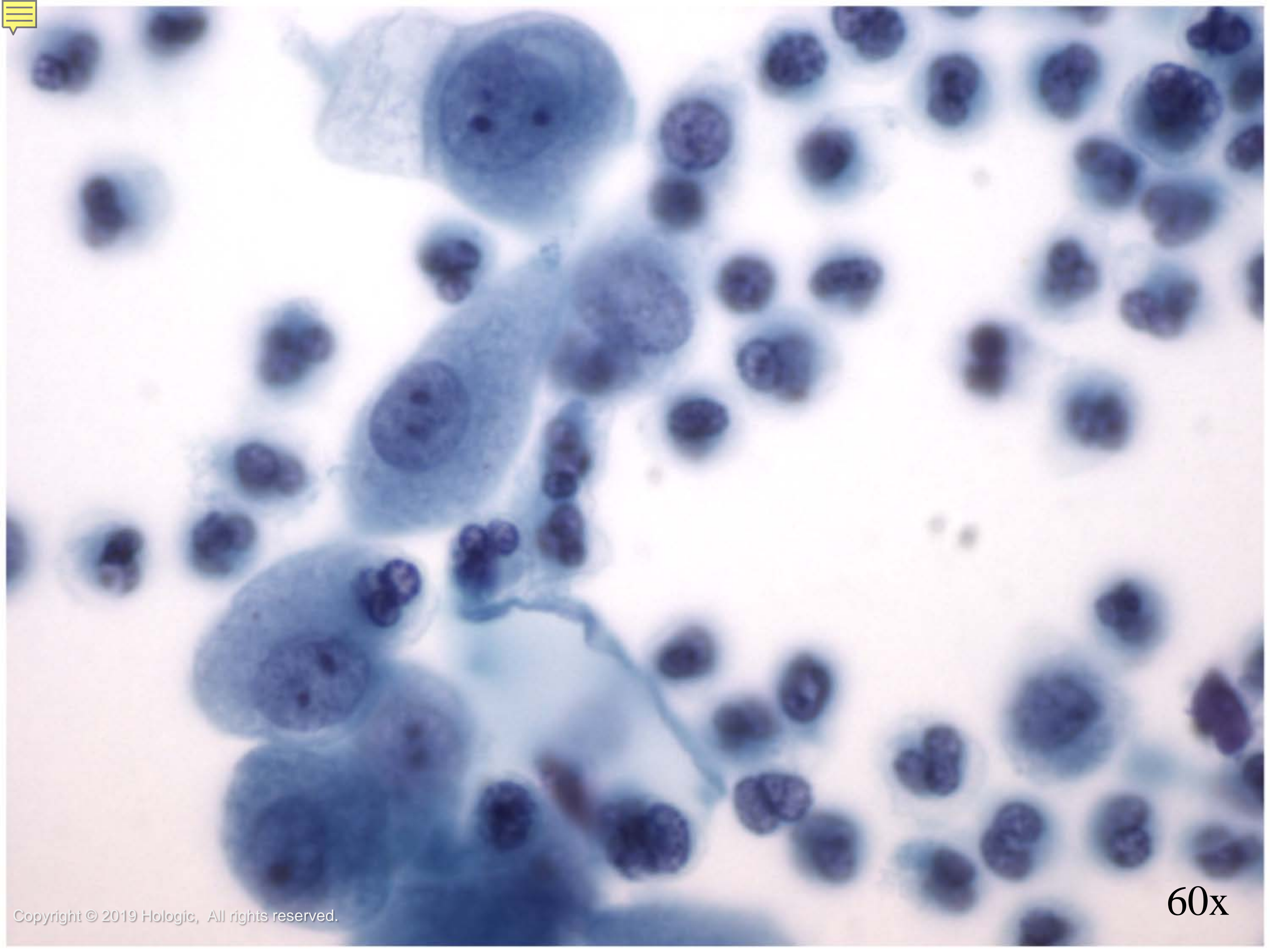

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Benign Entities and Changes

- Infectious agents that may be seen in specimens from the urinary tract may include:
  - Bacteria (most commonly *E. Coli* or streptococcus)
  - Candida
  - Polyoma Virus
  - CMV
  - Trichomonads

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Candida

- Candida may be in the form of spores and/or the traditional septate, branching filaments.
- It is very often seen as a contaminant from the female genital tract or external genitalia.
- It can be the source of an infection, especially in an immune compromised patient

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Polyoma Virus

- Polyoma virus can present a diagnostic challenge, as cells infected with the virus (decoy cells) can mimic malignancy
- Decoy cells are commonly plasmacytoid cells with eccentrically placed nuclei
- The virus causes a basophilic intranuclear inclusion, which often appears very dense and dark with a smooth nuclear membrane

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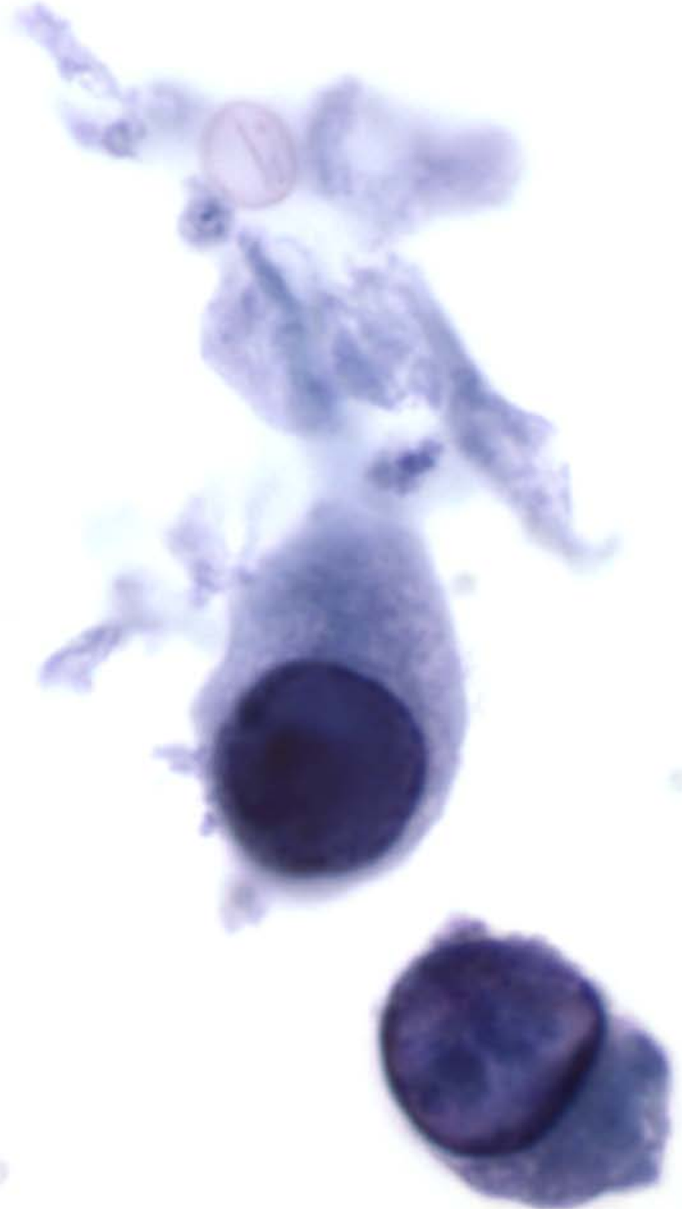

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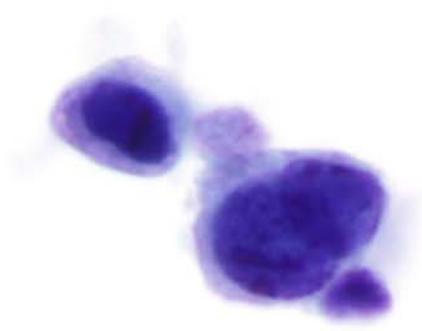

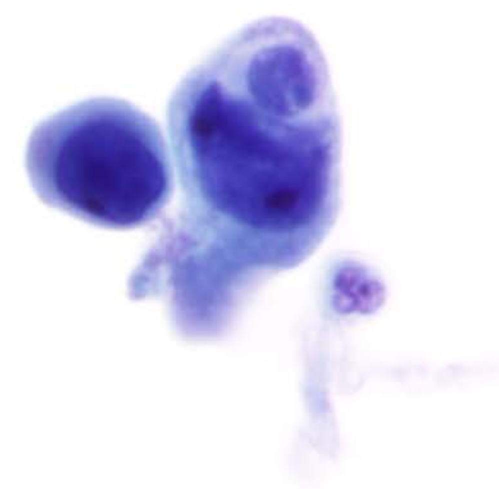

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Cytomegalovirus (CMV)

- This virus usually appears in patients with compromised immune systems or it may be transmitted from a mother to her fetus at birth.
- CMV infected cells typically have a large eosinophilic or basophilic intranuclear inclusion that causes margination of the nuclear chromatin, resulting in a “bull’s eye” appearance

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Trichomonas

- Trichomonads are an uncommon finding in urine and should be carefully discerned from degenerated PMNs.
- In a urinary specimen, the organism is usually round and bears its diagnostic eye spot, similar to that seen in Gyn samples.

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Diagnosis and Criteria

We will be utilizing *The Paris System for Reporting Urinary Cytology* for the sections covering diagnostic criteria and categorization

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Bladder Cancer in the US Statistics

- The 4th most common cancer in men[1]
- Estimated that 81,190 people will be diagnosed with bladder cancer in 2018 with an average age of 73 and an estimated 17,240 deaths[1]
- Men are 4 times more likely than women to be diagnosed with the disease. In addition, incidence rates in white men are double those of black men.[1]
- 5 year survival rates can range from 98% with stage 0 to 15% with stage IV[1]
- 708,444 survivors in need of screening in 2015[2]
- About 70% bladder cancers are superficial[3]

1. Cancer.net. ASCO.org sponsored. https://www.cancer.net/cancer-types/bladder-cancer/treatments-stage. Accessed June 25, 2018
2. National Cancer Institute. Surveillance, Epidemiology and End Results Program. Cancer Stat Facts: Bladder Cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed June 25, 2018.
3. UpToDate. Patient Educations Bladder Cancer treatment. https://www.uptodate.com/contents/bladder-cancer-treatment-non-muscle-invasive-superficial-cancer-beyond-the-basics. Accessed June 25, 2018

Bladder Cancer in the US
Treatment

- Early-stage bladder cancer is treated locally with surgical excision during cystoscopy
- Bacillus Calmette-Guerin (BCG) is a standard immunotherapy drug for high grade non-invasive bladder cancer
- Cystectomy is the removal of the bladder, used for invasive or recurrent tumors
- Advanced bladder cancer is often treated with intravesical or systemic chemotherapy

Cancer.net. ASCO.org sponsored. https://www.cancer.net/cancer-types/bladder-cancer/treatments-stage. Accessed June 25, 2018

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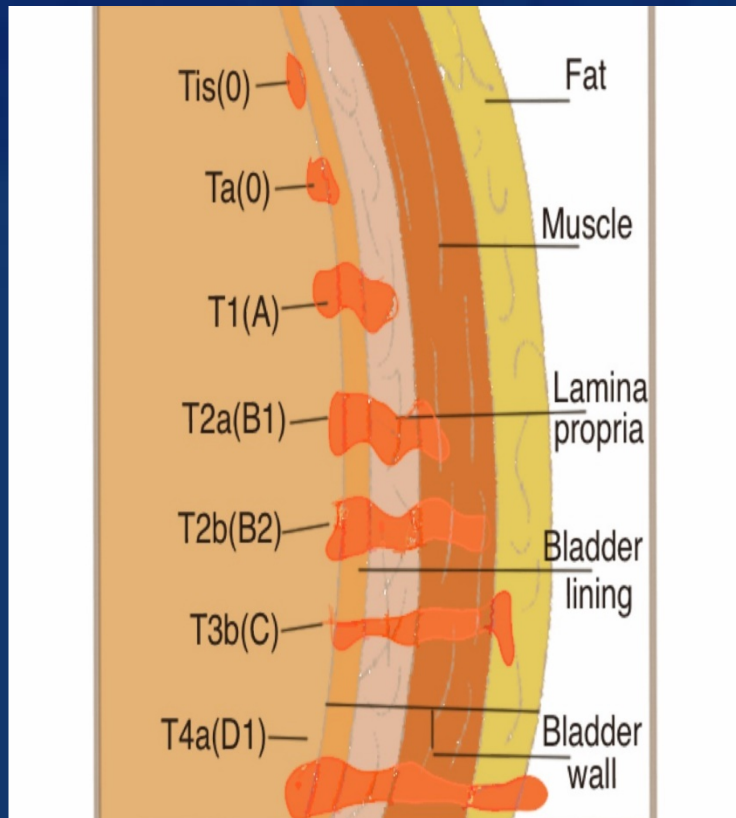
Bladder Cancer in the US
Prognosis

- Low grade bladder tumors are more likely to be cured[1]
- High grade bladder tumors are more likely to recur *and* progress[1]
- Taking all superficial bladder tumors together, about 65% will recur in the first 2 years but mainly as early non-invasive bladder cancer[2]
- About 30% will recur as more serious disease with less chance of cure or control[2]
- Treated patients are followed with cystoscopy at regular (typically 3 month) intervals and any new tumors visualized are removed surgically[3]

1. Rosenthal DL, Wojcik EM, Kurtycz DF. Pathogenesis of Urothelial Carcinoma In: *The Paris System for Reporting Urinary Cytology*. Springer International Publishing Switzerland; 2016.
2. Rosenthal DL, et al, eds. High Grade Urothelial Carcinoma (HGUC). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:61-74 :1-4. . Rosenthal DL, et al, eds. Clinical Management. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:143-151.
3. Rosenthal DL, et al, eds. Clinical Management. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:143-151.

Bladder Cancer Staging



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TNM Classification	Jewett-Strong Marshall	Definition
Tis	0	Limited to mucosa, flat insitu
Ta	0	Limited to mucosa, papillary
T1	A	Lamina propria invaded
T2a	B1	< halfway through muscularis
T2b	B2	> halfway through muscularis
T3	C	Perivesical fat
T4a	C	Prostate, uterus or vagina
T4b	C	Pelvic wall or abdominal wall
N1-N3	D1	Pelvic lymph node(s) involved
M1	D2	Distant metastases

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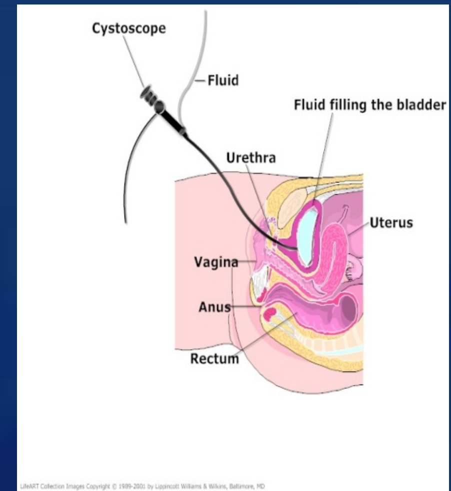
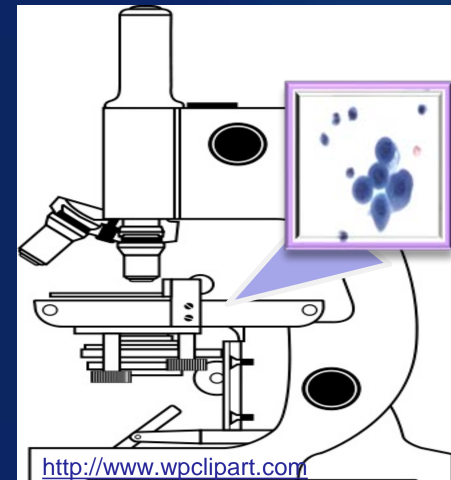
Diagnosis and Monitoring

Cystoscopy: The gold standard for diagnosis and monitoring

Post treatment	Frequency
0-2 years:	Every 3 months
2-4 years:	Every 6 months
5-or more years:	Yearly



Cytology: Performed as an adjunct test to cystoscopy, often on bladder washings



Aldousari S, Kassouf W. Update on the management of non-muscle invasive bladder cancer. Can Urol Assoc J. 2010 Feb; 4(1): 56–64

The Paris System for Reporting Urinary Cytology: Rationale

- Main goal of urinary cytology is to find and diagnose high grade lesions
- Current lack of reproducibility and lack of sensitivity for low grade lesions
- There is a need to standardize and educate clinicians on terminology
- Wide interobserver variability for atypical cells- national atypical rates vary among institutions

Rosenthal DL, et al, eds. *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016.

The Paris System for Reporting Urinary Cytology: Pathogenesis - Two Pathways

The current understanding is that there are two different pathogenetic pathways:

- Hyperplasia
- Dysplasia

The molecular abnormalities associated with these two pathways indicate that these pathways are distinct and separate, and confer separate risks of progression to malignancy

Rosenthal DL, et al, eds. Pathogenesis of Urothelial Carcinoma. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:1-4.

The Paris System for Reporting Urinary Cytology: Pathogenesis - Two Pathways

Hyperplasia

- 80% of urothelial carcinomas use this pathway
- Starts as hyperplasia that progresses to low-grade papillary urothelial carcinoma (LGUC)
- Genetically stable pathway
- Characterized by FGFR3 alterations (fibroblast growth factor receptor 3)
- High recurrence rate
- Nonaggressive behavior
- Currently accepted progression rate to HGUC is at 10% and new studies have pointed to the rate being much lower (< 1-6%)

Rosenthal DL, et al, eds. Pathogenesis of Urothelial Carcinoma. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:1-4.

The Paris System for Reporting Urinary Cytology: Pathogenesis - Two Pathways

Dysplasia

- Found to be the pathway for 20% of urothelial carcinomas
- Genetically unstable pathway associated with multiple mutations including TP53
- Dysplasia progresses to a high-grade papillary tumor or less often to a flat urothelial carcinoma (carcinoma in situ)
- High recurrence rate and a high risk of muscle-invasive, stage T2, T3, and T4 tumors with lymph node and systemic metastasis

Rosenthal DL, et al, eds. Pathogenesis of Urothelial Carcinoma. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:1-4.

The Paris System for Reporting Urinary Cytology: Adequacy Algorithm

Source of disagreement and controversy

Numerous variables can effect adequacy. This algorithm considers the variables that effect the usefulness of the specimen to diagnose the suspicion of urothelial carcinoma

- Collection type
- Cellularity
- Volume
- Cytomorphological findings (considered first)

Rosenthal DL, et al, eds. Adequacy of Urine Specimens (Adequacy). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:5-11.

The Paris System for Reporting Urinary Cytology: Adequacy Algorithm (cont.)

Cytomorphologic features:

- Presence of atypical or malignant cells

Specimen type:

- Voided urine- greater than 30 mL more likely adequate
- Instrumented- cellularity 2600 cells- 20 urothelial cells/10 high power fields
- Presence of excessive and obscuring lubricant, inflammatory cells, or red blood cells should be interpreted as unsatisfactory/nondiagnostic

Rosenthal DL, et al, eds. Adequacy of Urine Specimens (Adequacy). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:5-11.

The Paris System for Reporting Urinary Cytology: Adequacy Algorithm (cont.)

Atypical, Suspicious, or Malignant
No
Yes
Instrumented
No
Yes
Appropriate Benign Urothelial Cellularity*
Non-Urothelial Features Obscuring Urothelial Morphology
Yes
No
No
Yes
Adequate Volume
No
Appropriate Benign Urothelial Cellularity*
No
Inadequate
Adequate
Yes
Yes

Reproduced from: Rosenthal DL, et al, eds. Adequacy of Urine Specimens (Adequacy). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:5-11.

"*": Cut-offs for appropriate benign urothelial cellularity should be validated for both instrumented and non-instrumented sources

The Paris System for Reporting Urinary Cytology Criteria: Categories

- Negative for High-Grade Urothelial Carcinoma (NHGUC)
- Atypical Urothelial Cells (AUC)
- Suspicious for High-Grade Urothelial Carcinoma (SHGUC)
- High-Grade Urothelial Carcinoma (HGUC)
- Low-Grade Urothelial Neoplasia (LGUN)
- Other Malignancies Primary and Metastatic and Miscellaneous Lesions

Rosenthal DL, et al, eds. Contents. In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:xiii.

Approach to Diagnosis in Urinary Tract

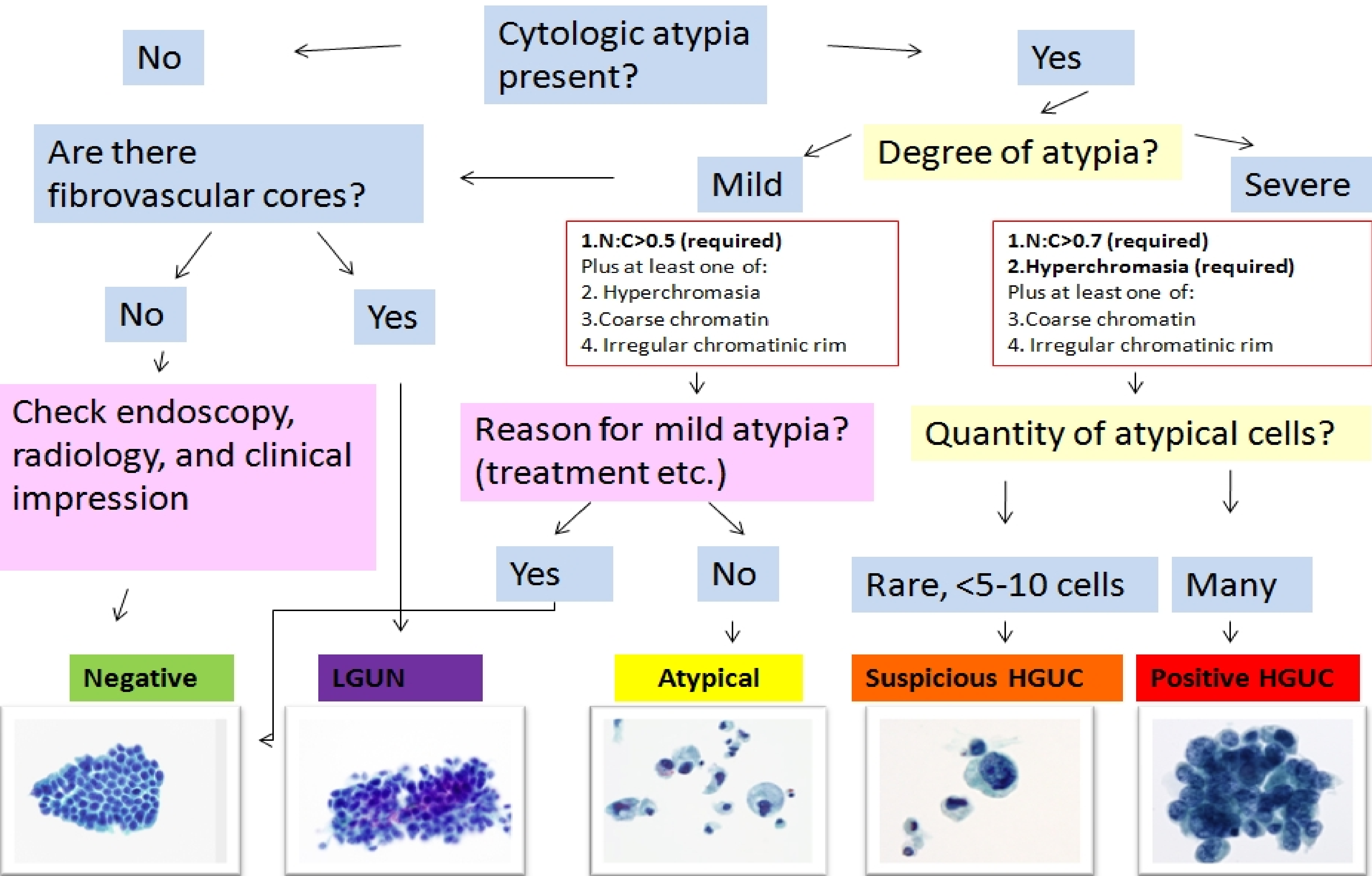
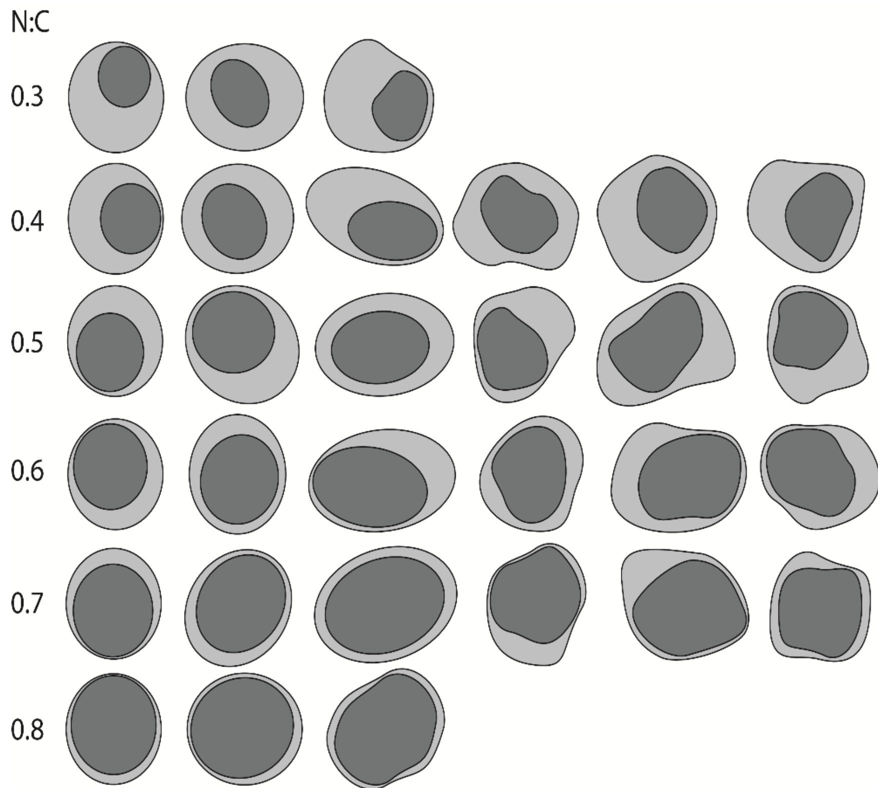


Diagram by Guliz Barkan, MD. Permission Granted by Eva M. Wojcik, MD

Nuclear:Cytoplasmic Ratio



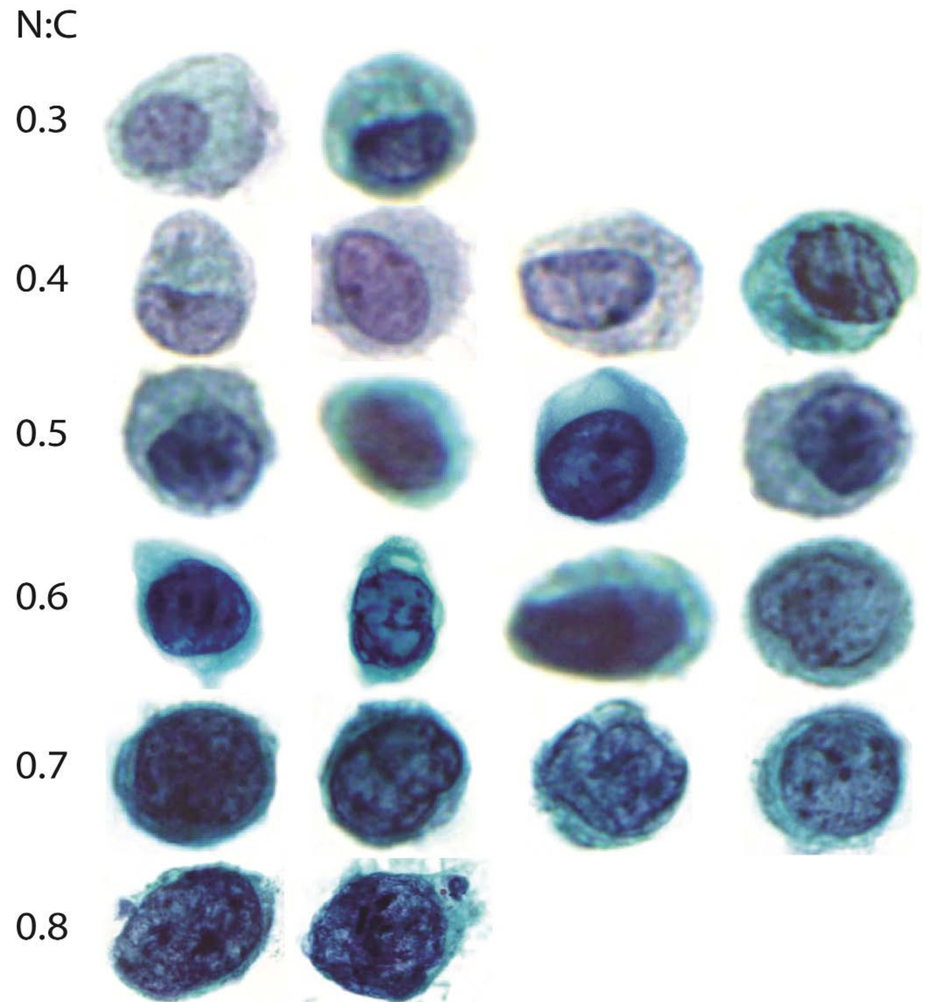


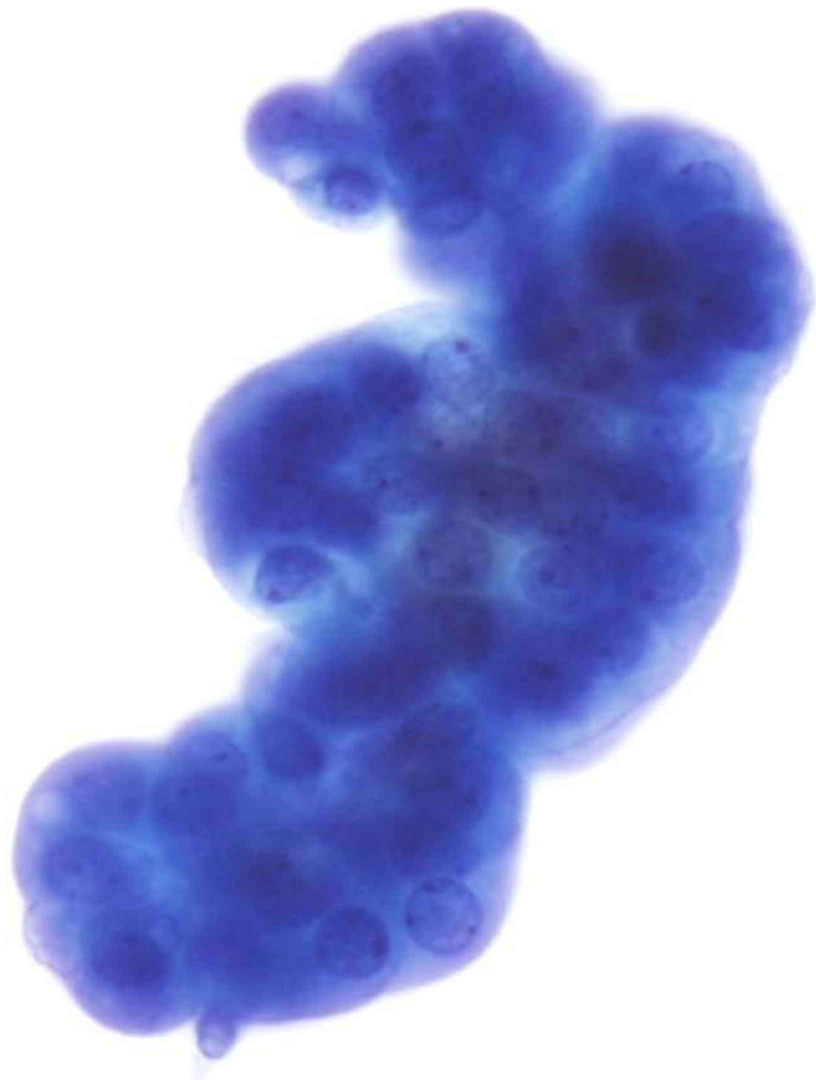
Diagram by Lisa Zhang, MD. Permission Granted by Eva M. Wojcik, MD

The Paris System for Reporting Urinary Cytology: Diagnostic Categories & Criteria

Benign Findings – either voided or instrumented:

- Benign urothelial, glandular, and squamous cells
- Benign urothelial tissue fragments (BUTF) and urothelial sheets or clusters
- Changes associated with lithiasis
- Viral cytopathic effect: polyoma virus (BK virus- decoy cells)
- Post therapy effect, including epithelial cells from urinary diversions

Rosenthal DL, et al, eds. Negative for High Grade Carcinoma (Negative). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:13-38.



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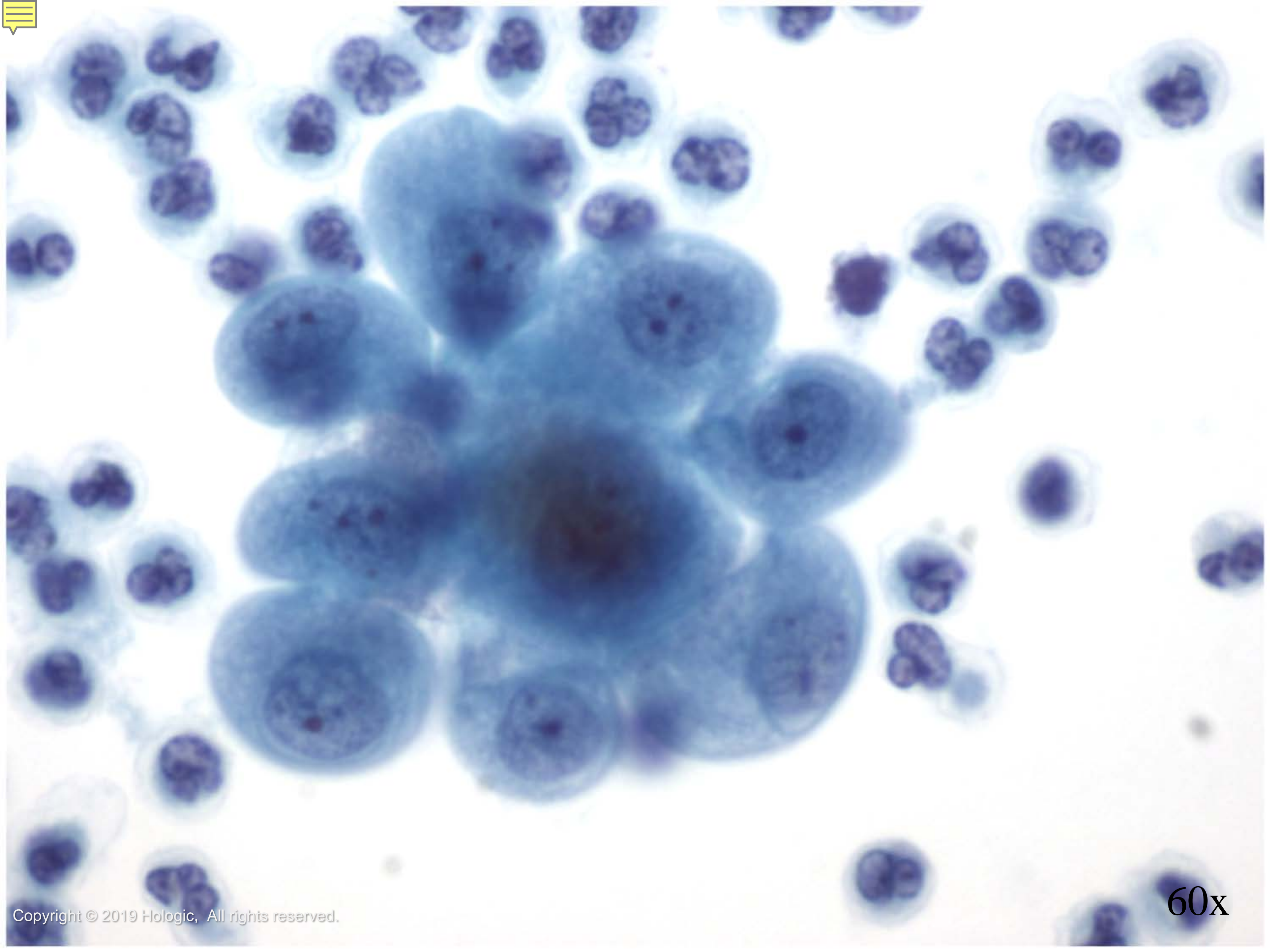

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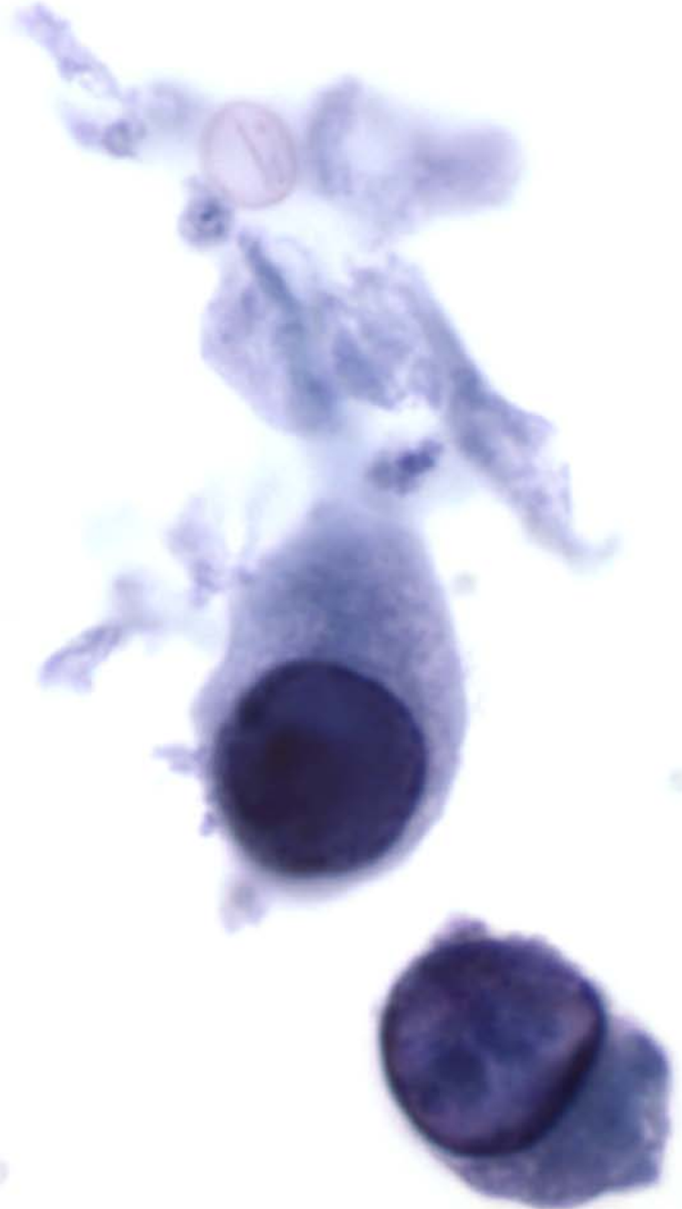

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The Paris System for Reporting Urinary Cytology: Diagnostic Categories & Criteria

Atypical Urothelial Cells (AUC)

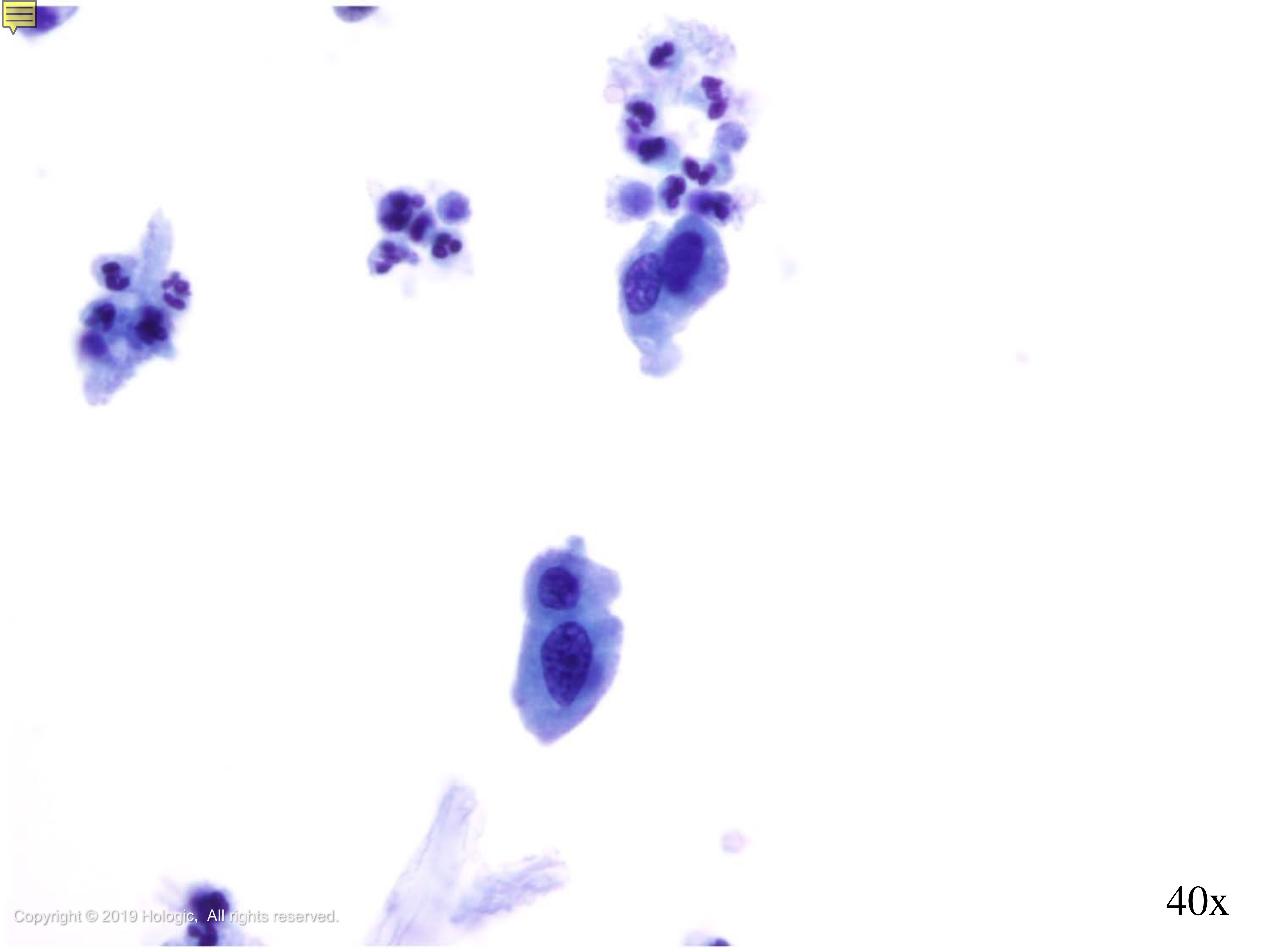
The abnormal urothelial cells must be non-superficial and non-degenerated as well as display:

- Increased nuclear cytoplasmic ratio of >0.5 (if this is the only finding, the case should not be reported in the AUC category)

In addition, one of the minor criteria below must also be displayed:

- Nuclear hyperchromasia (without being so pronounced as that of cells in the SHGUC or HGUC category)
- Irregular nuclear membranes (typically displaying an irregular nuclear shape and variably thickened chromatinic rim, while remaining round, not oval in shape)
- Irregular, coarse, clumped chromatin

Rosenthal DL, et al, eds. Atypical Urothelial Cells (AUC). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:39-48.



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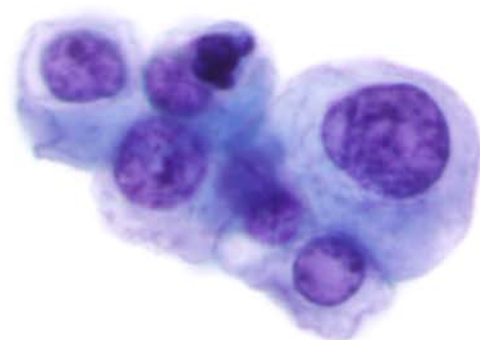

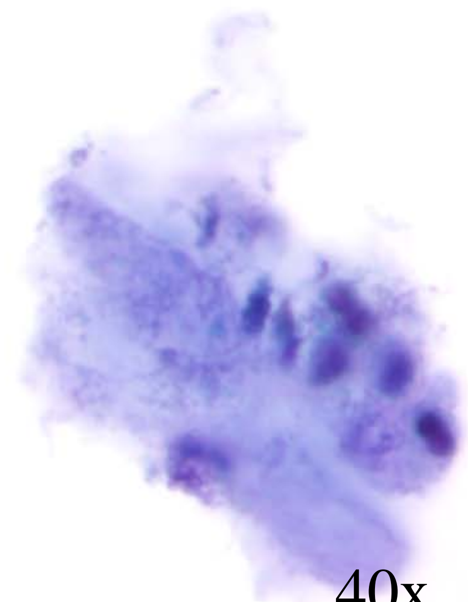

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The Paris System for Reporting Urinary Cytology: Diagnostic Categories & Criteria

Suspicious for High Grade Urothelial Carcinoma (SHGUC)

Must display both required criteria below:

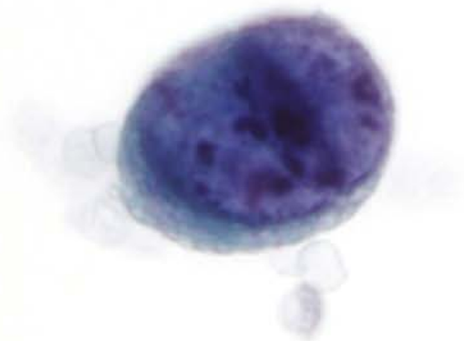
- Increased N/C ratio of at least 0.5-0.7
- Moderate to severe hyperchromasia

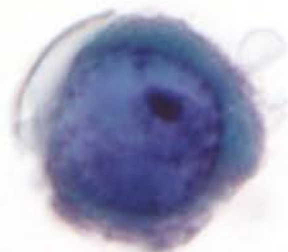
In addition to above criteria, must also display either or both of the criteria below:

- Irregular clumpy chromatin
- Marked irregular nuclear membranes

The number of abnormal cells, previous history of HGUC and collection method should all be taken into consideration. 5-10 cells are recommended for the diagnosis of HGUC with 10 being the recommended number in instrumented specimens. SHGUC can be used restrictively for cases that do not meet that quantity, being careful not to render a diagnosis by applying criteria to degenerated cells.

Rosenthal DL, et al, eds. Suspicious for High Grade Urothelial Carcinoma (Suspicious). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:49-60.





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The Paris System for Reporting Urinary Cytology: Diagnostic Categories & Criteria

High Grade Urothelial Carcinoma (HGUC)

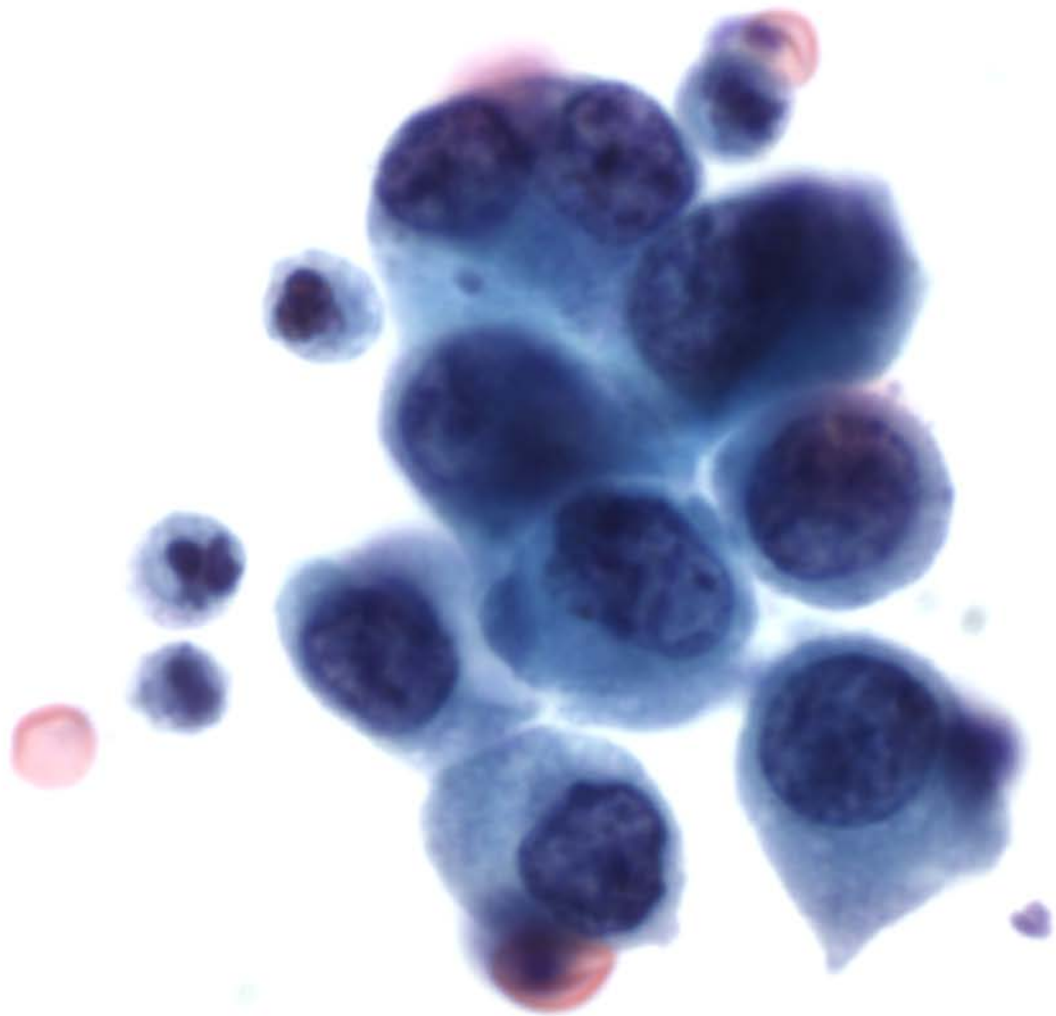
Malignancy criteria:

- At least 5-10 abnormal cells
- N/C ratio is $\geq$ 0.7 (majority of HGUC cells with some showing a range of 0.5-0.7)
- Moderate to severe hyperchromasia
- Markedly irregular nuclear membrane
- Coarse/clumped chromatin

Other features:

- Pleomorphism with marked variation in cellular size and shape
- Scant, pale, or dense cytoplasm
- Prominent nucleoli
- Mitoses
- Necrotic debris
- Inflammation

Rosenthal DL, et al, eds. High Grade Urothelial Carcinoma(HGUC). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:61-74.



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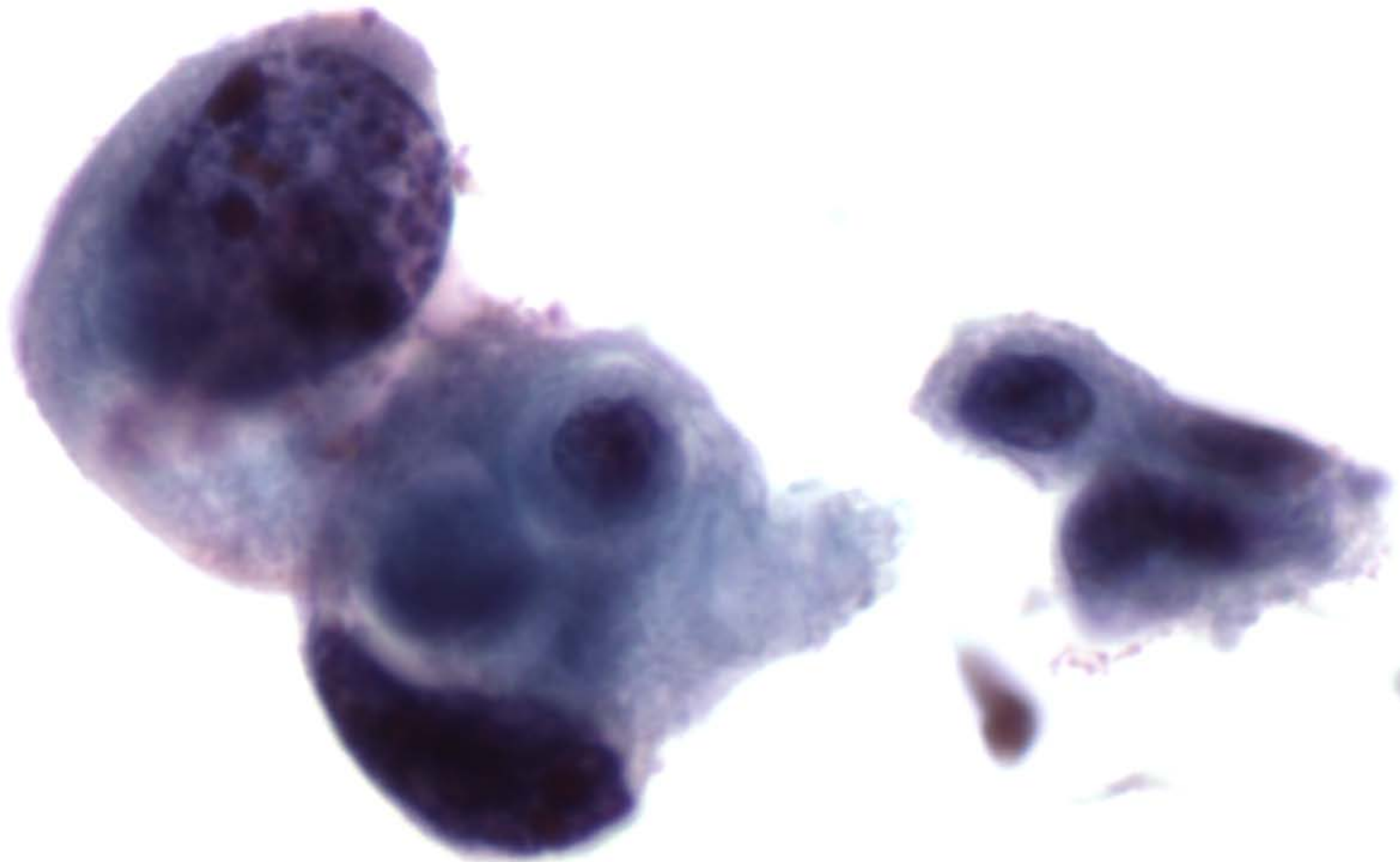

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The Paris System for Reporting Urinary Cytology: Low-Grade Urothelial Neoplasia (LGUN) Facts

- The distinction between low-grade lesions and normal epithelium is extremely difficult
- This diagnosis can be rarely made and should be based *only* on the presence of well-defined fibrovascular cores in the absence of cellular atypia.
- LGUN is a cytologic term which combines:
  - Low grade papillary lesions:
    - urothelial papilloma
    - PUNLMP
    - LGPUC
  - Flat, low-grade intraurothelial neoplasia

Rosenthal DL, et al, eds. Low Grade Urothelial Carcinoma (LGUN). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:75-86.

The Paris System for Reporting Urinary Cytology: Diagnostic Categories & Criteria

Low Grade Urothelial Neoplasm (LGUN)

Regardless of the specimen type (voided or instrumented):

- Three-dimensional papillary clusters, defined as clusters of cells with nuclear overlapping, forming papillae WITH fibrovascular cores including capillaries. The presence of this feature is the only time a definitive diagnosis of LGUN is possible. This finding is exceedingly rare.

LGUN may be considered (particularly with correlation in biopsy or cystoscopic findings which should be reported as a note on the report whenever possible) BUT be categorized as NHGUC in the presence of these cytologic features:

- Three-dimensional cellular clusters *without* fibrovascular cores
- Increased numbers of monotonous single (non-umbrella) cells

The features below were previously reported as criteria for LGPUC and may also be associated with HGUC. Without other HGUC features these changes may suggest a LGUN lesion BUT be categorized as NHGUC:

- Cytoplasmic homogeneity
- Nuclear border irregularity
- Increased N/C ratio

Rosenthal DL, et al, eds. Low Grade Urothelial Carcinoma (LGUN). In: *The Paris System for Reporting Urinary Cytology*. Cham, Switzerland: Springer International Publishing; 2016:75-86.

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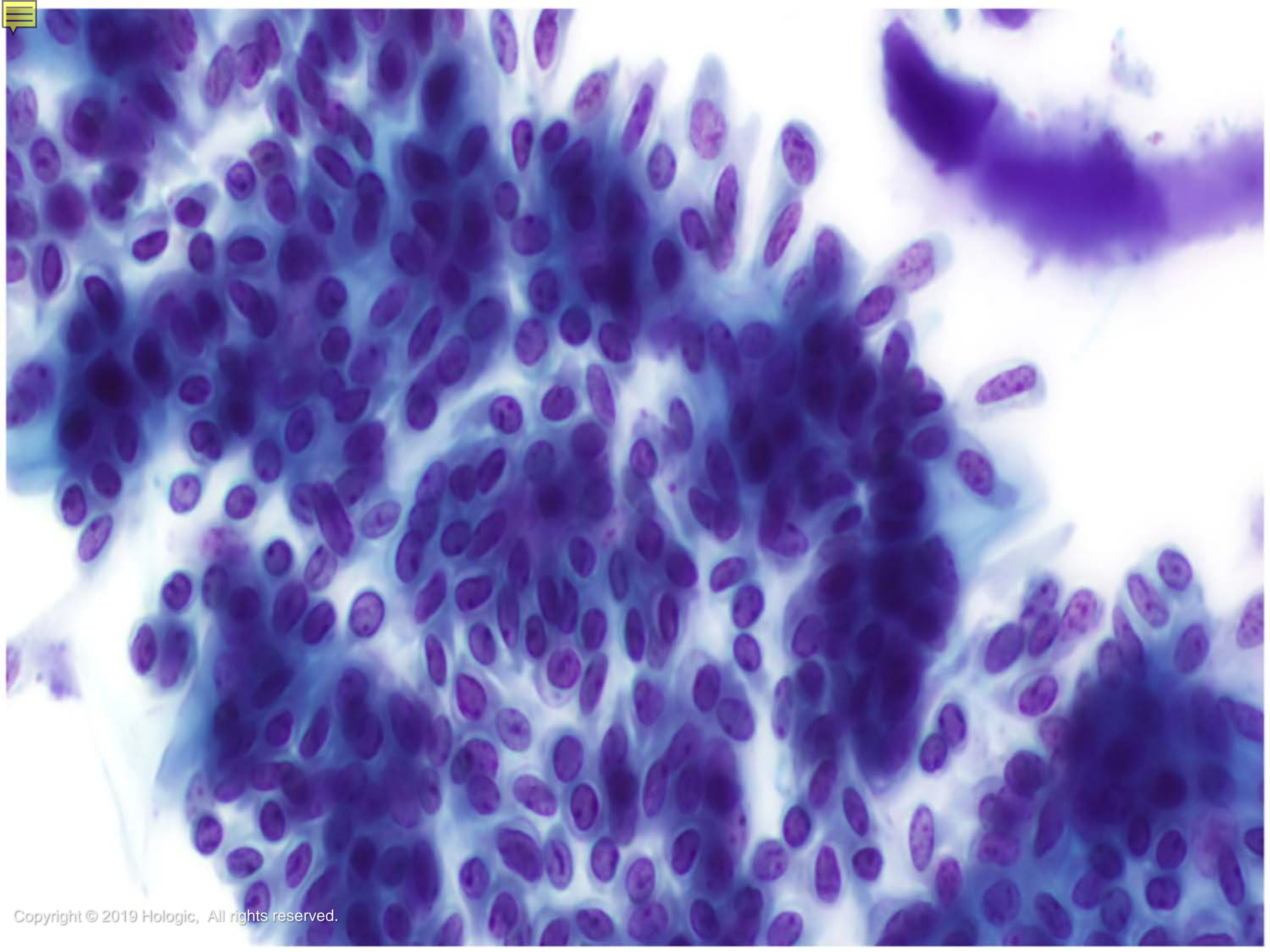
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Squamous Cell Carcinoma

- Relatively rare in the United States
- Strong association with Schistosomiasis
- Marked nuclear pleomorphism with dense hyperchromatic nuclei and macronucleoli. Abundant cytoplasm that may form spindle and tadpole shapes. Keratin pearls, intercellular bridges and keratohyalin granules may be seen.
- To help distinguish from HGUC with squamous differentiation, look for the presence of abnormal urothelial cells
- Non-keratinized squamous carcinomas may be more difficult to distinguish from HGUC.

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Adenocarcinoma

- Bladder
  - Rare, accounting for <2% of bladder cancers
  - Features include three-dimensional clusters of round, vacuolated cells with large, eccentrically placed, irregular nuclei with open chromatin and prominent nucleoli

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Adenocarcinoma

- Kidney
  - Only sheds into urine in end stage disease
  - Typically, cells are round with vacuolated cytoplasm and may be degenerated
  - Nuclei are large and round with prominent nucleoli
  - Appearance may vary according to differentiation of tumor

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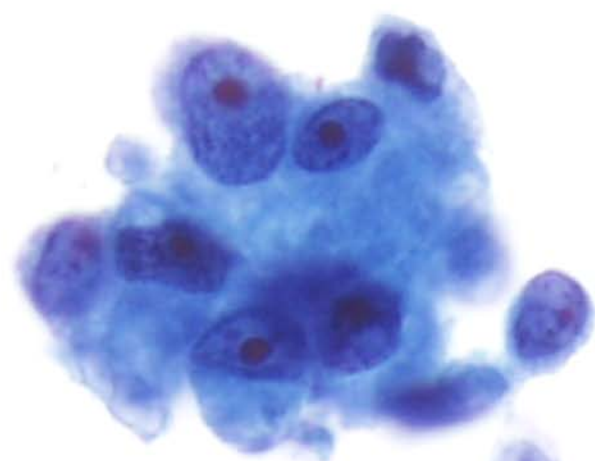
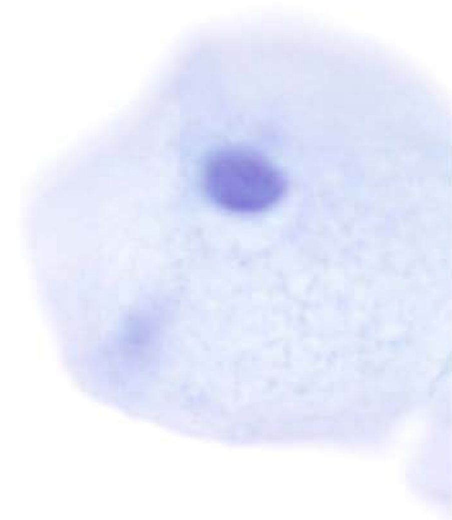

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Adenocarcinoma

- Prostate:
  - May shed after instrumentation (especially of prostate) or when disease has invaded bladder
  - May present as clusters or single cells
  - Typically is characterized by loose clusters of glandular cells with eccentric nuclei and prominent nucleoli
  - May show cytoplasmic mucin vacuoles

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Fluorescence In Situ Hybridization (FISH)

- Used for the Detection and Monitoring of Urothelial Carcinoma
- Technique which maps the presence or absence of targeted genomic sequences in chromosomes using fluorescent probes
- The targeted genes within the chromosomes are then detected using a fluorescent microscope

Cibas ES, Ducatman BS. Urine and Bladder Washings - Ancillary Techniques. In: *Cytology - Diagnostic Principles and Clinical Correlates.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2009:123-124.

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UroVysion Bladder Cancer FISH Assay

- Additional testing method for the initial detection of bladder cancer in patients with hematuria suspected of having bladder cancer and monitoring for recurrence
- Detects aneuploidy in chromosomes 3, 7, 17 and the loss of 9p21 locus using Fluorescence In Situ Hybridization

Cibas ES, Ducatman BS. Urine and Bladder Washings - Ancillary Techniques. In: *Cytology - Diagnostic Principles and Clinical Correlates.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2009:123-124.

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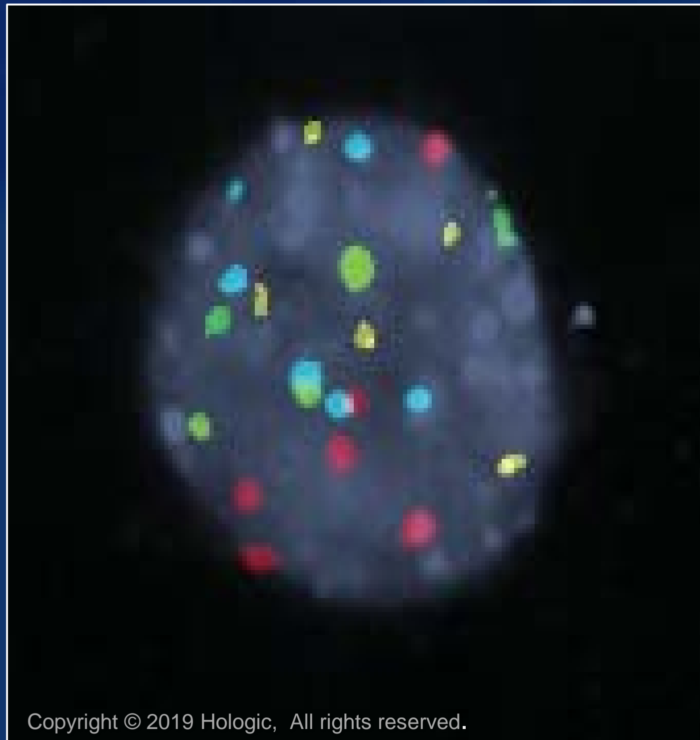
Urine Processed by UroCyte® Method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