Weill Cornell Medicine
Pathology & Laboratory Medicine

A Pathologist's Perspective on Prostate Cancer:

Why Morphology Under the Microscope Matters

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“Healing begins with a diagnosis”

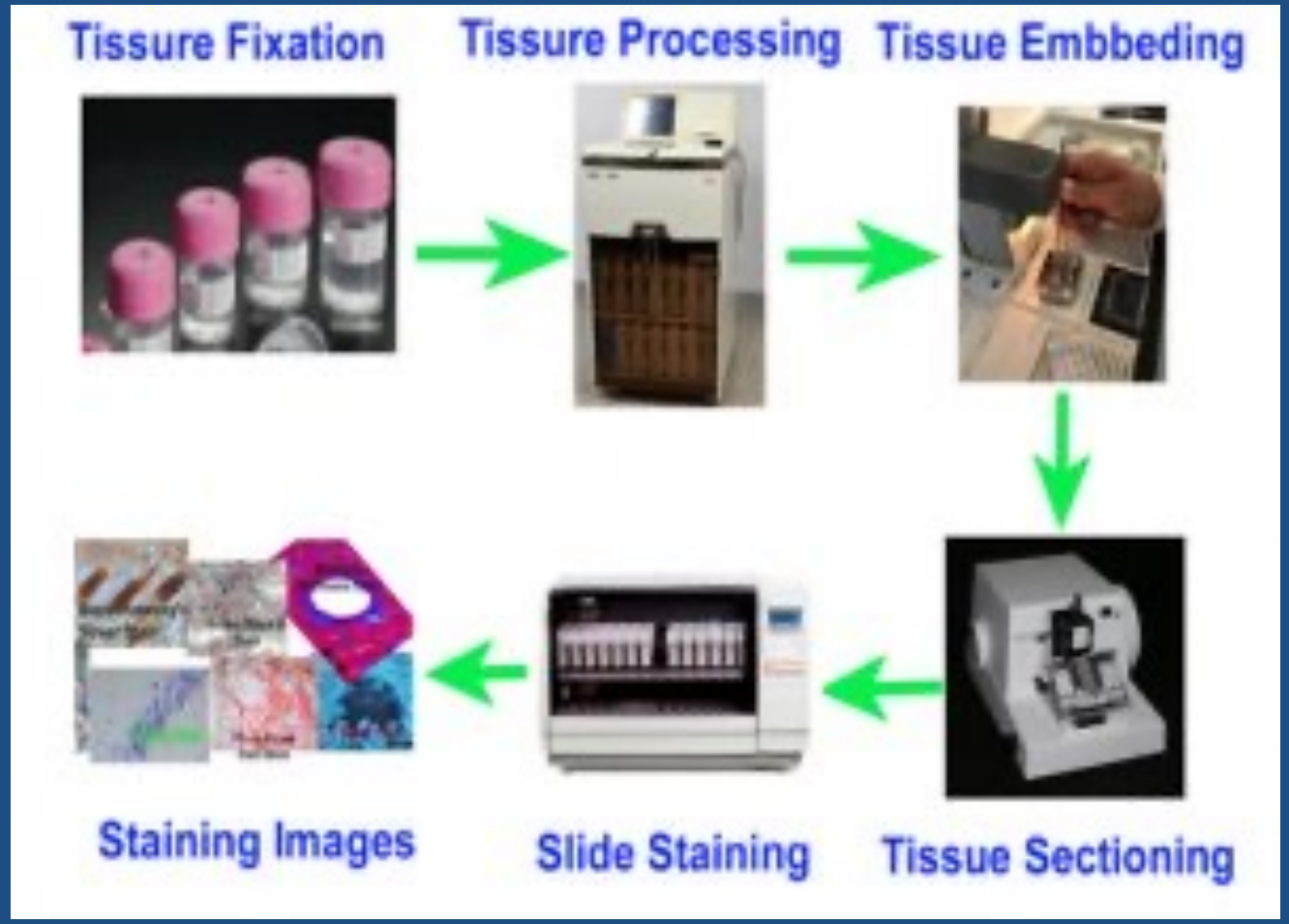
- Broadly, “**pathology**” refers to the *study of disease*
- **Pathologists** are physicians who work in a laboratory to examine samples of body tissue for diagnostic purposes
- Pathologists play a critical role in determining an appropriate treatment plan for patients

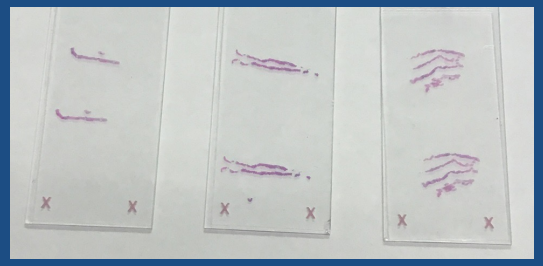
Pathologists diagnose all cancers…How?

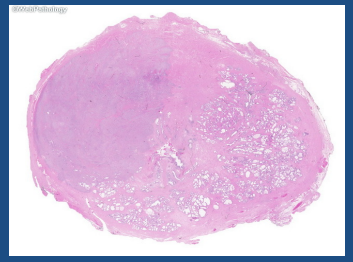
- By looking at slides with human tissue under a microscope

How are these slides created?

- Prostate biopsy
- Prostatectomy

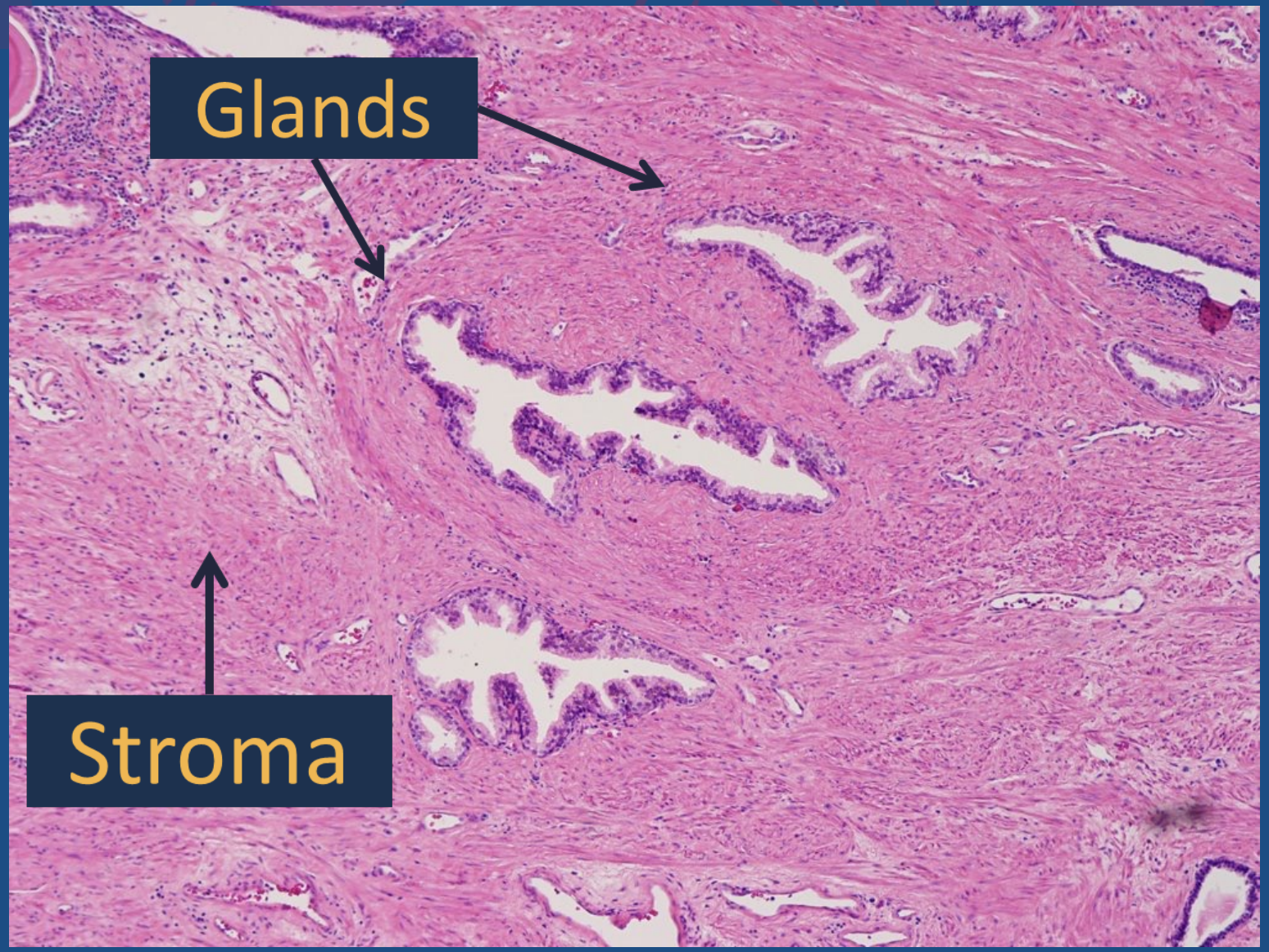




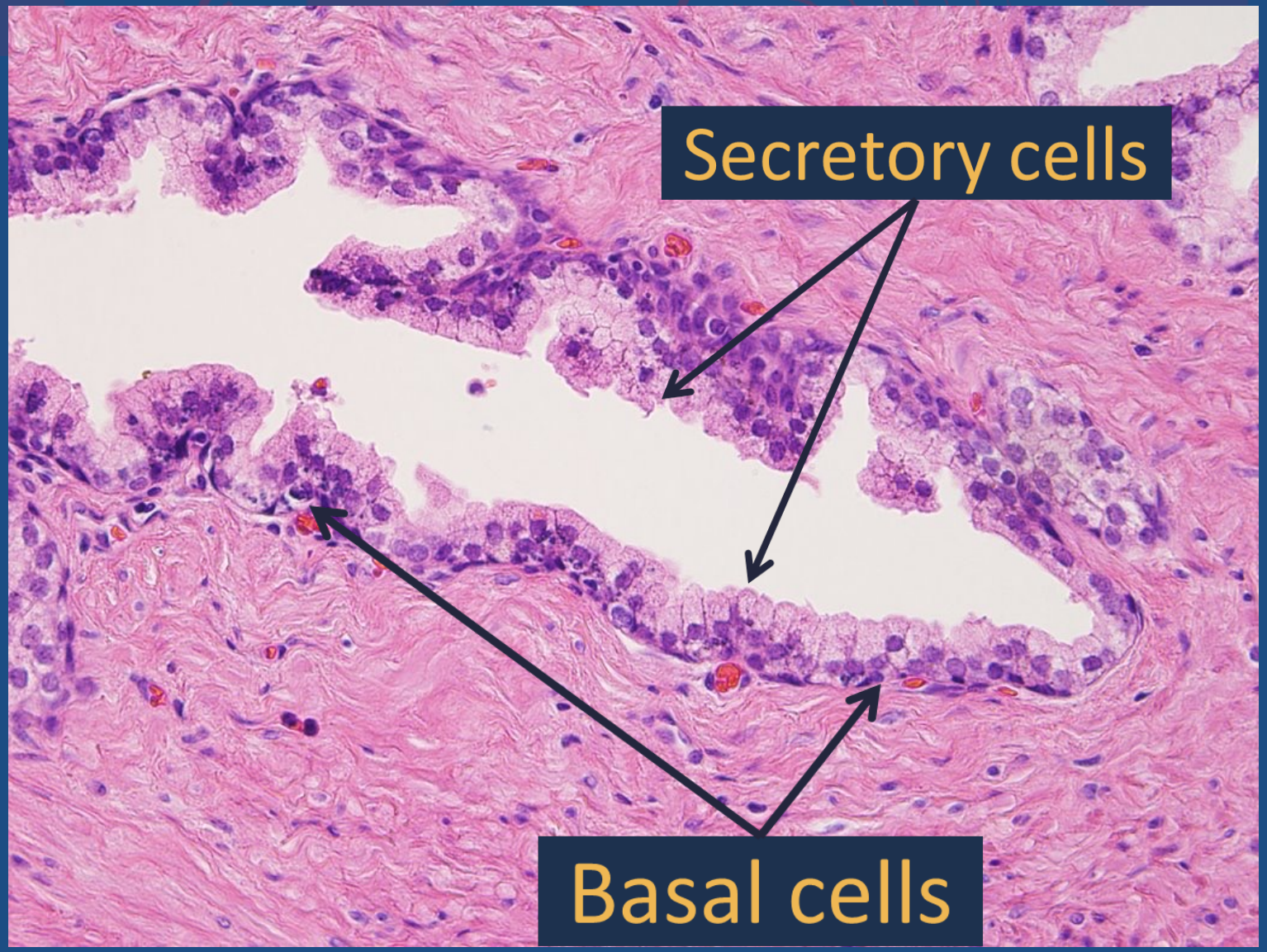


https://vitrovivo.com/histopathology-and-laser-capture-microdissection-services/

Normal Prostate Tissue



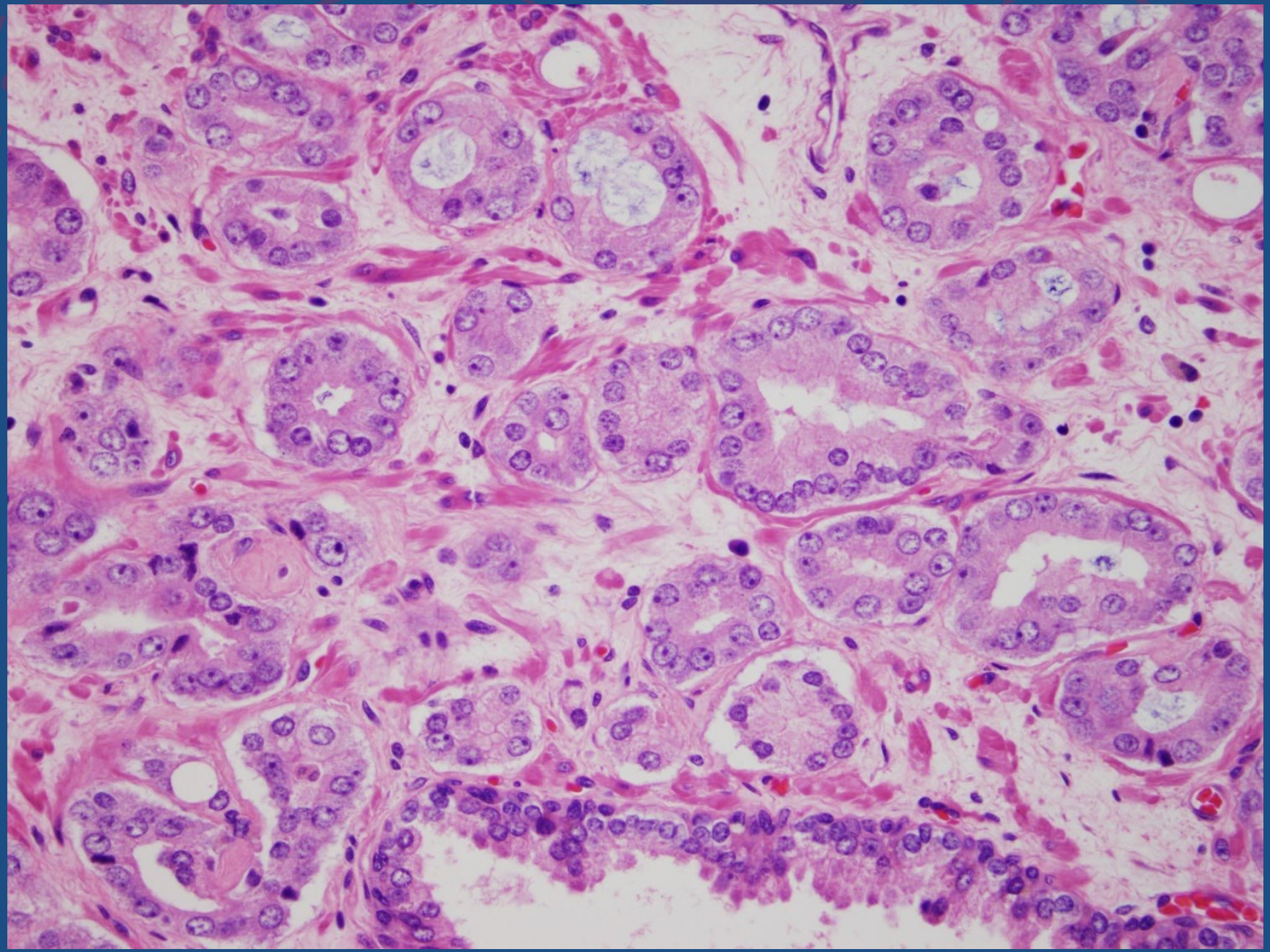
Benign prostate glands: 2 cell layers



Prostate cancer

- Basal cell layer absent; only single layer of (cancerous) secretory cells present

- •Normal architecture (distribution) of glands is disrupted by invasive cancer glands
- – Cancer glands are crowded and infiltrative



Key Factor in Determining Treatment

- Prostate cancer **GRADING** (done by pathologists only!)

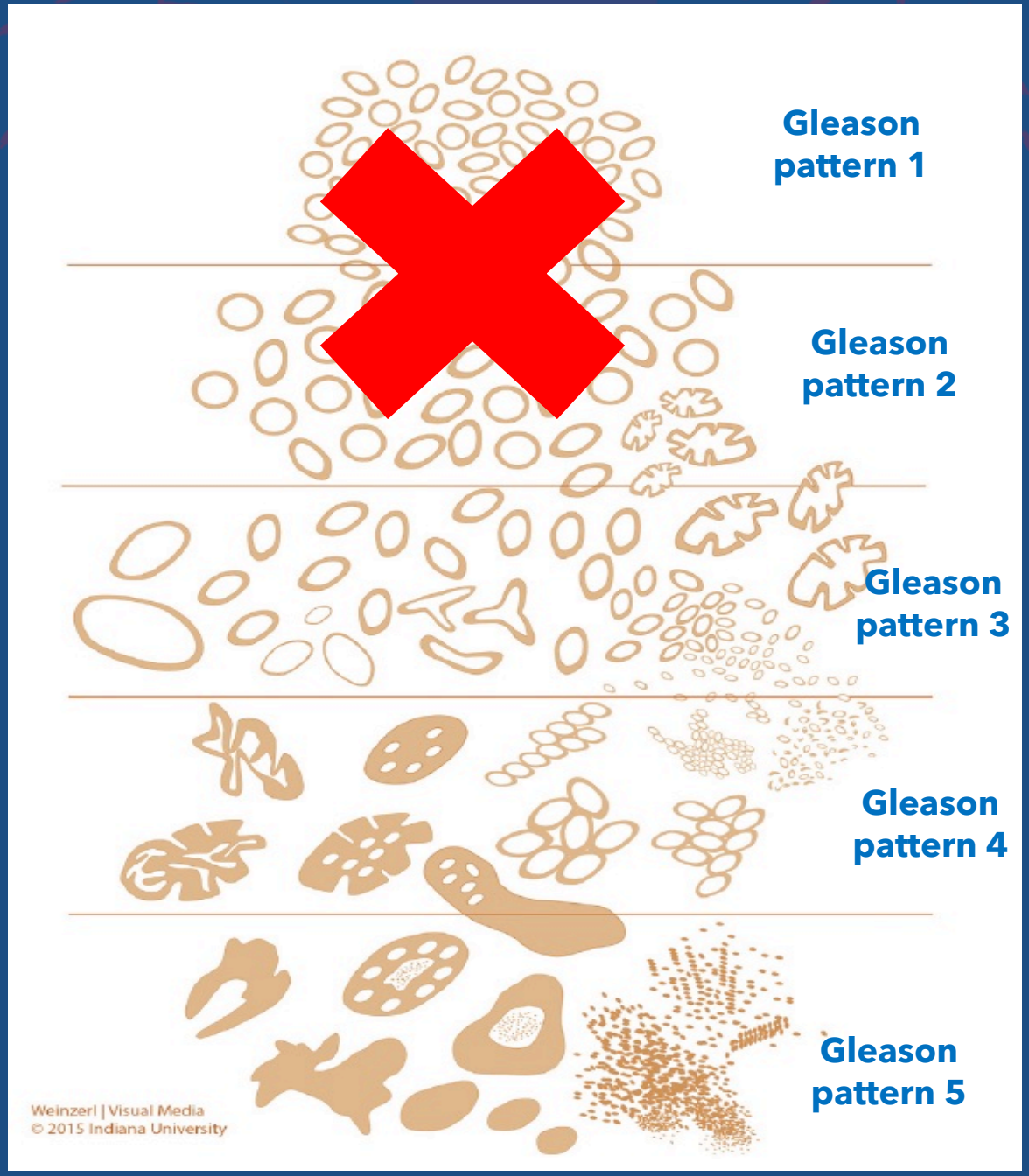
- *What do we mean by "grade"?*

  - Grade of cancer reflects its "differentiation"- meaning the degree to which the cancer resembles normal prostate glands

  - Pathologists evaluate prostate cancer morphology under the microscope to determine the grade

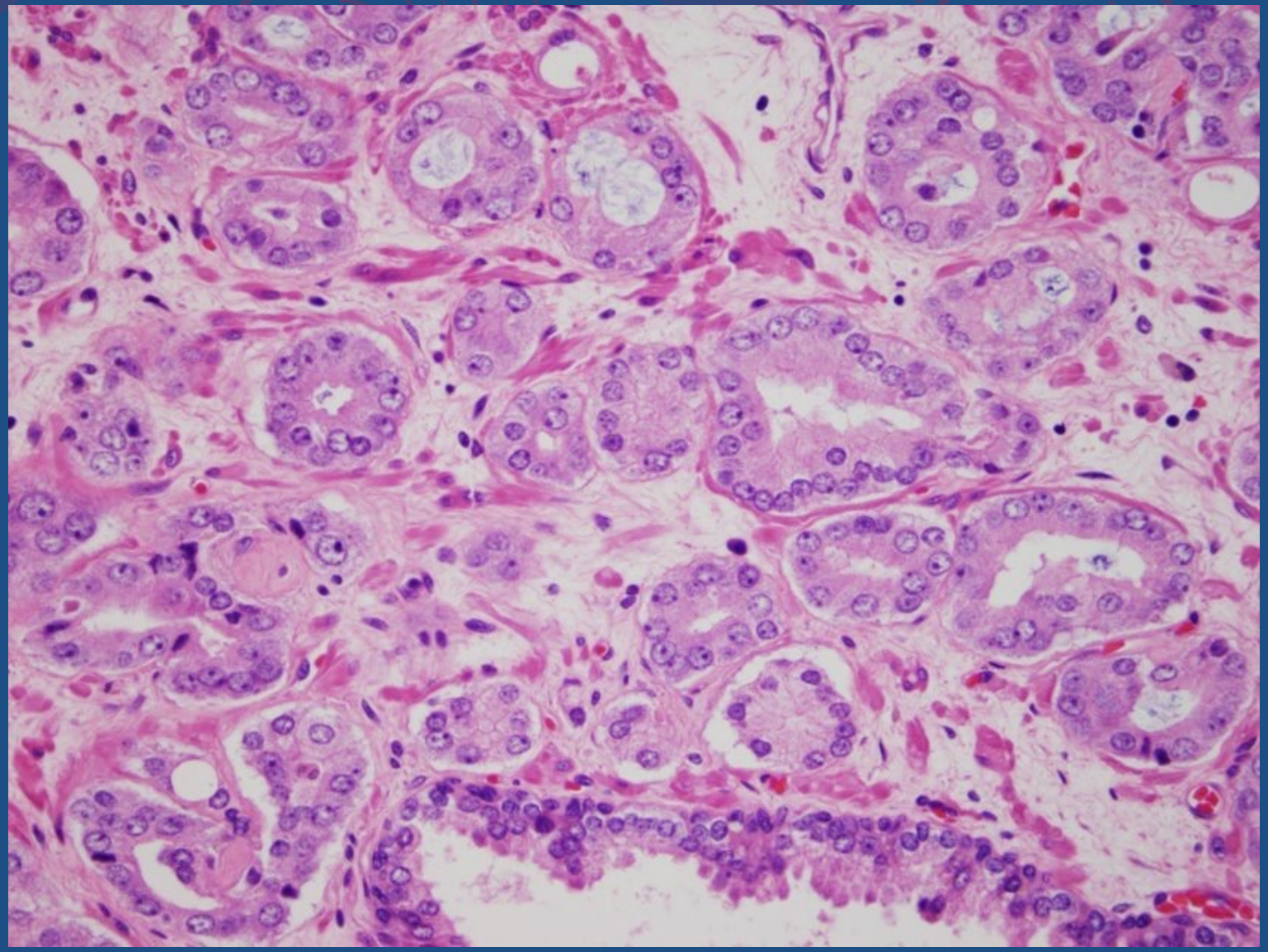
Prostate Cancer Grading

- Graded with Gleason Grading System
- Gleason patterns 3, 4, and 5 represent prostate cancer



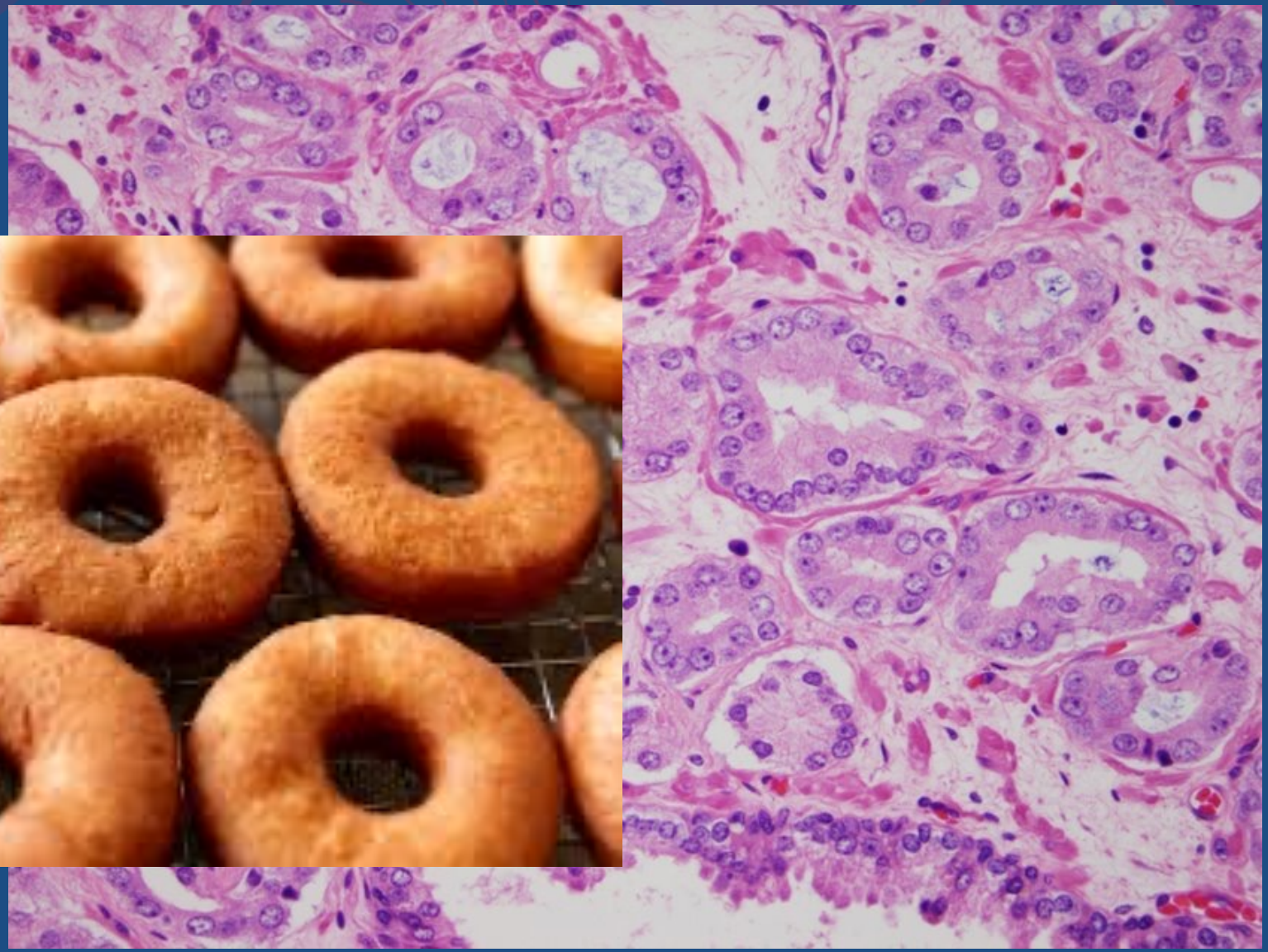
Grading prostate cancer

- Gleason pattern 3



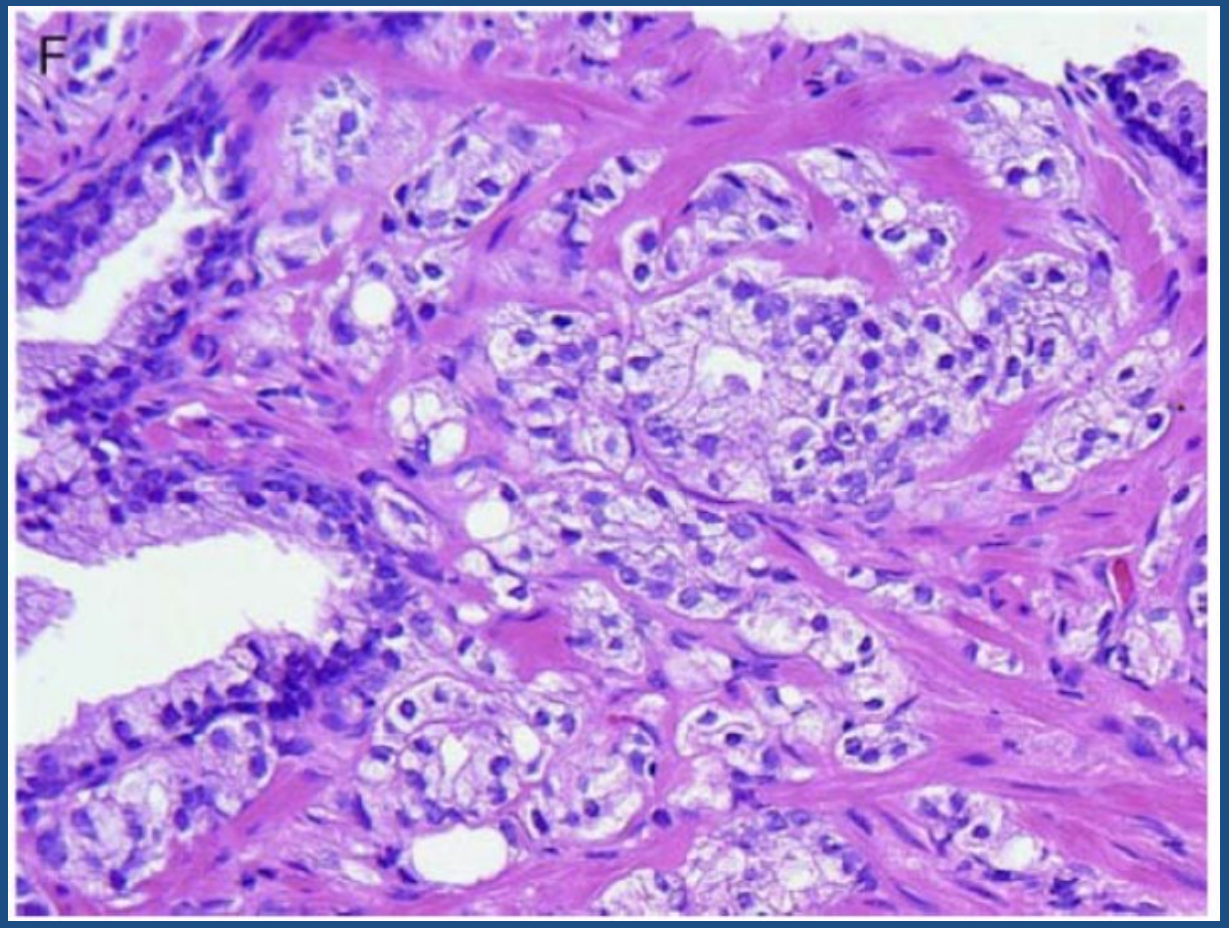
Grading prostate cancer

- Gleason pattern 3



Grading prostate cancer

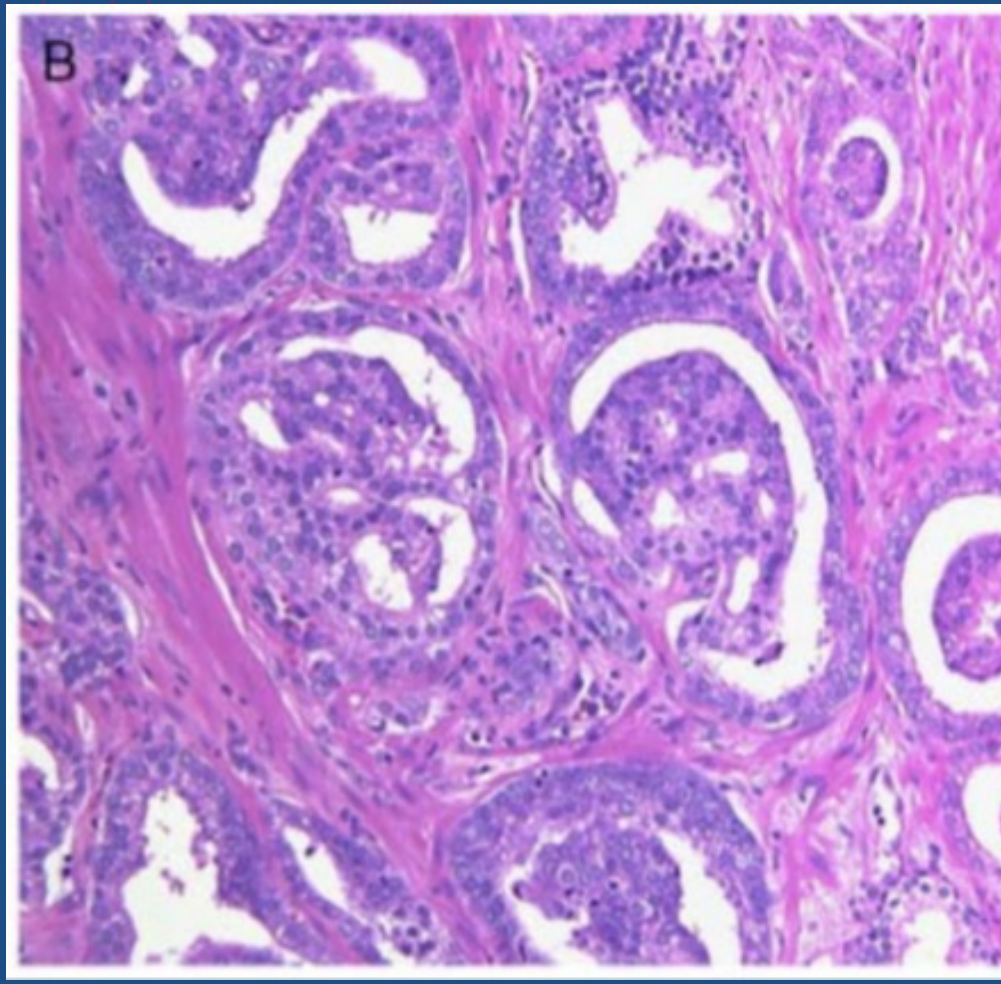
- Gleason pattern 4
  - - poorly formed /fused glands



Grading prostate cancer

- Gleason pattern 4

- - glomeruloid



Grading prostate cancer

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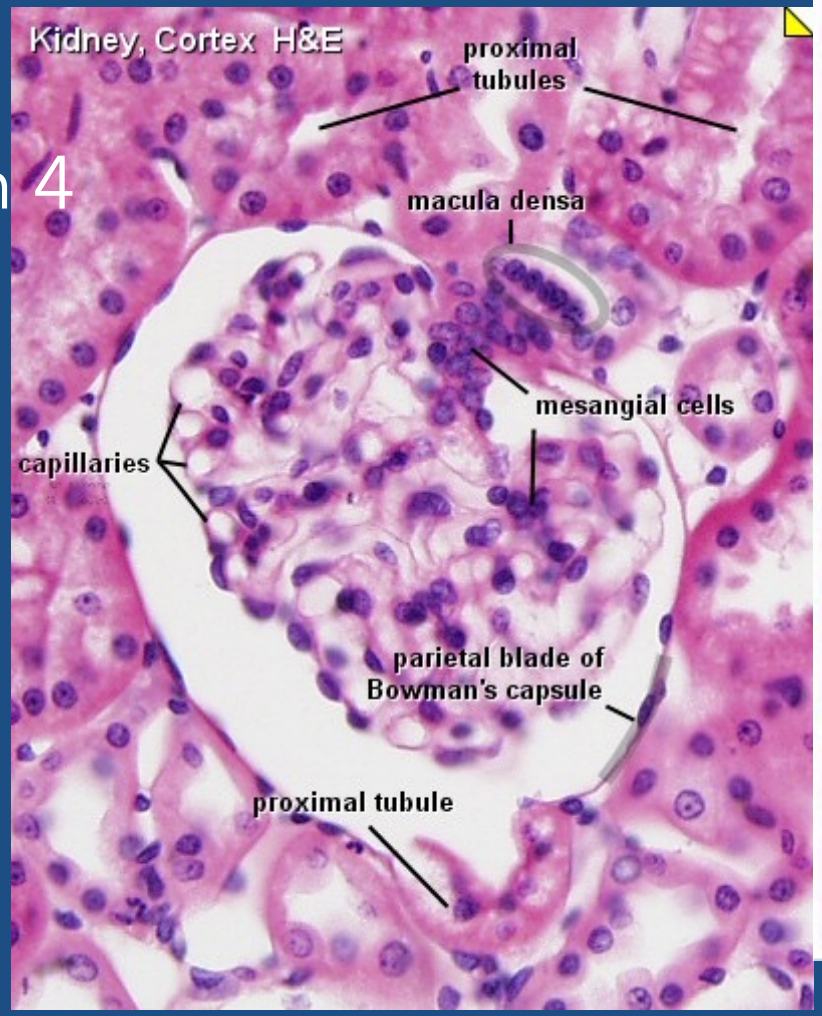
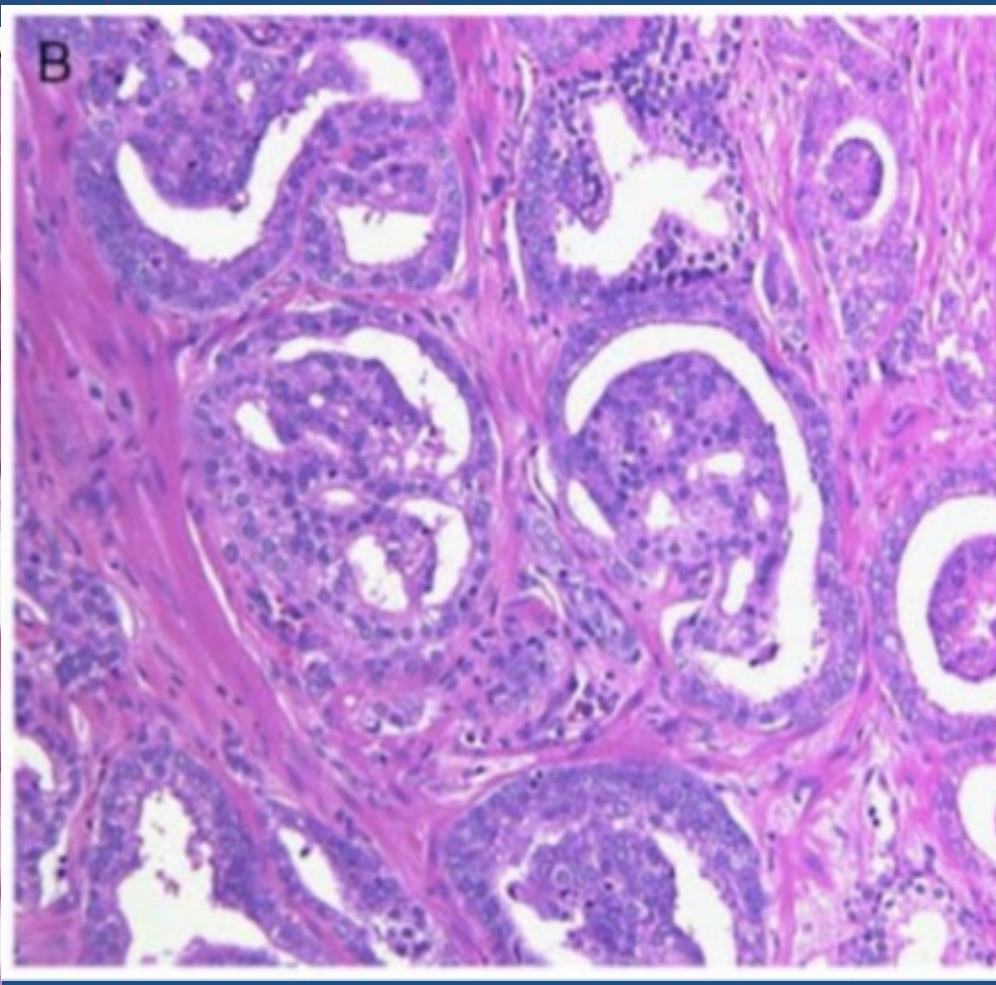
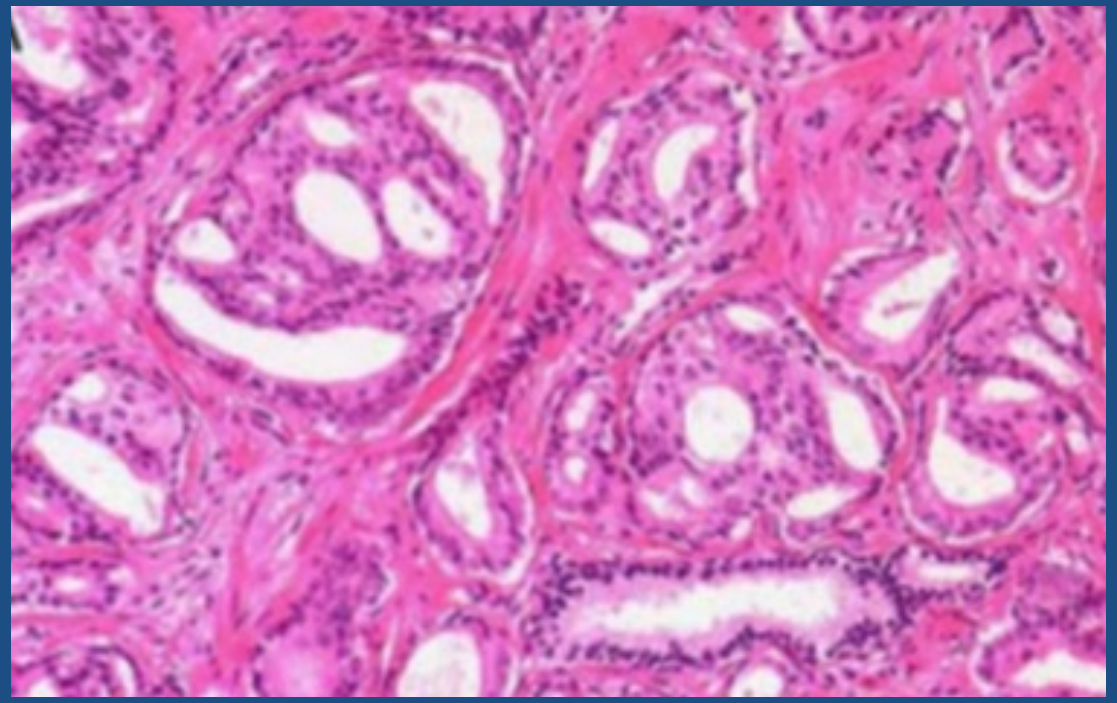




Grading prostate cancer

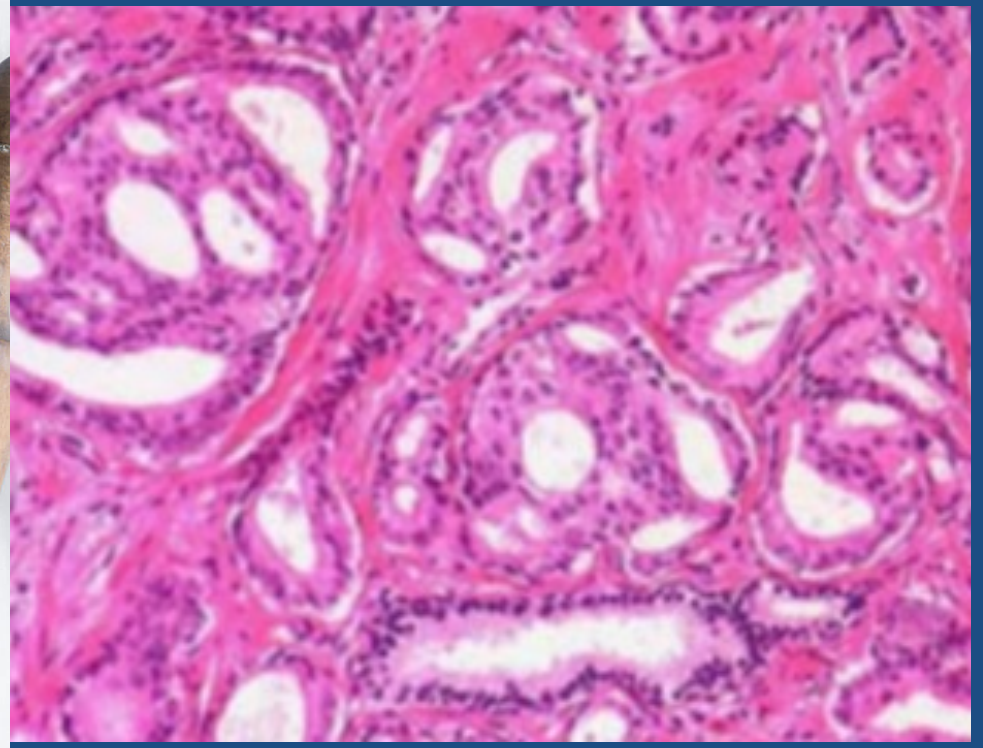
- Gleason pattern 4

- - cribriform



Grading p r

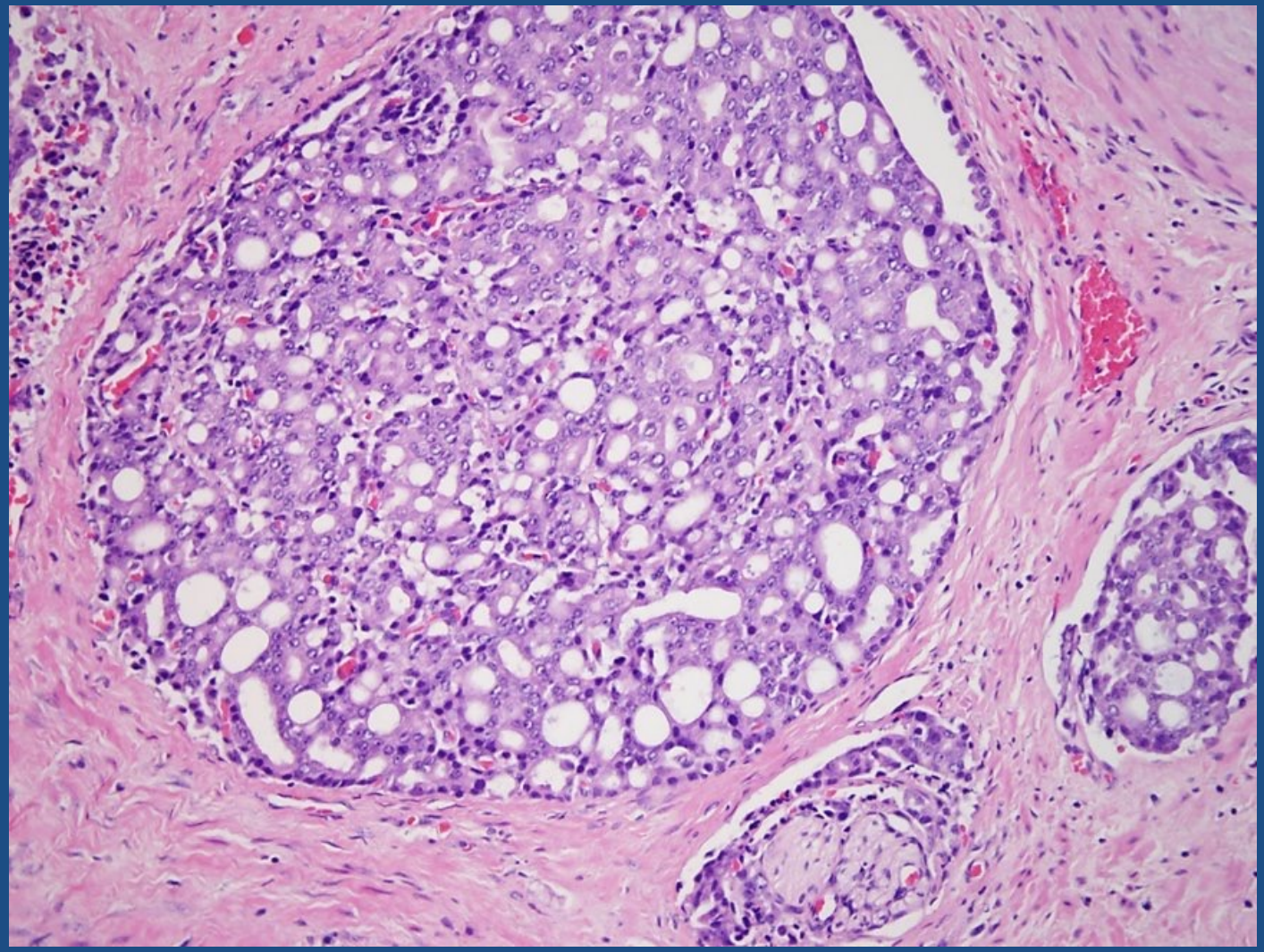
- Gleason patte



Grading prostate cancer

- Gleason pattern 4

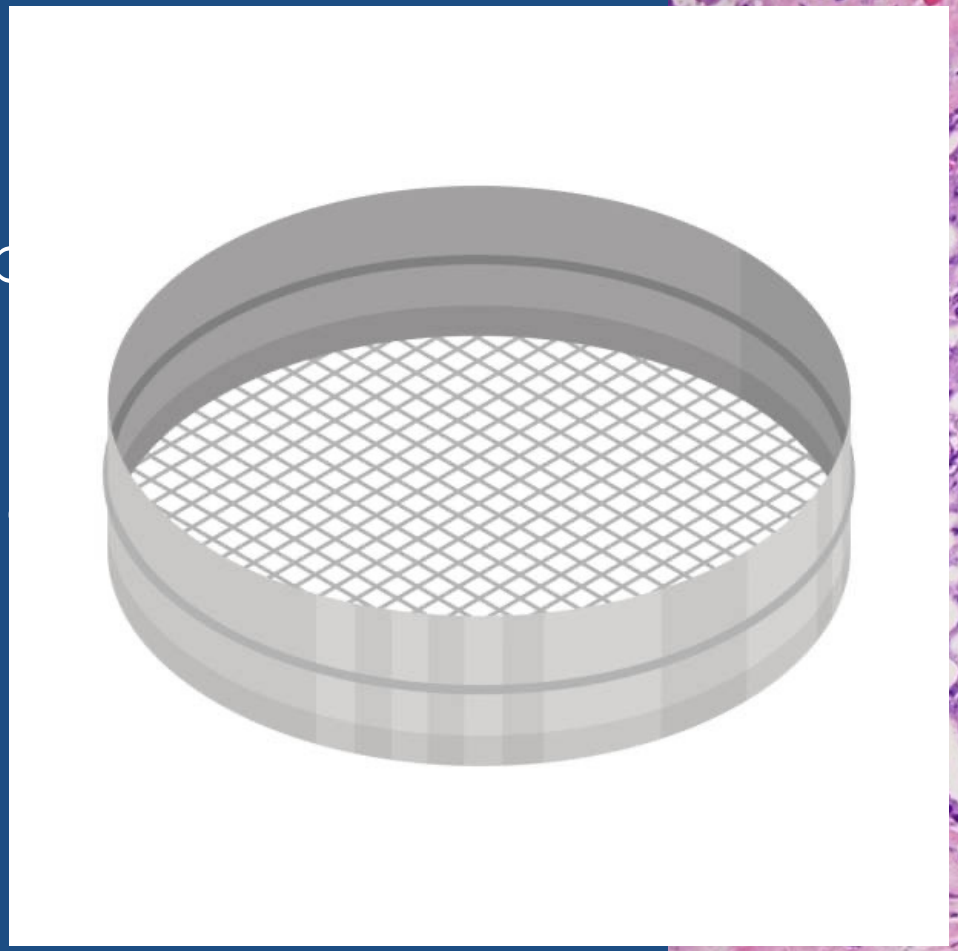
  - large cribriform

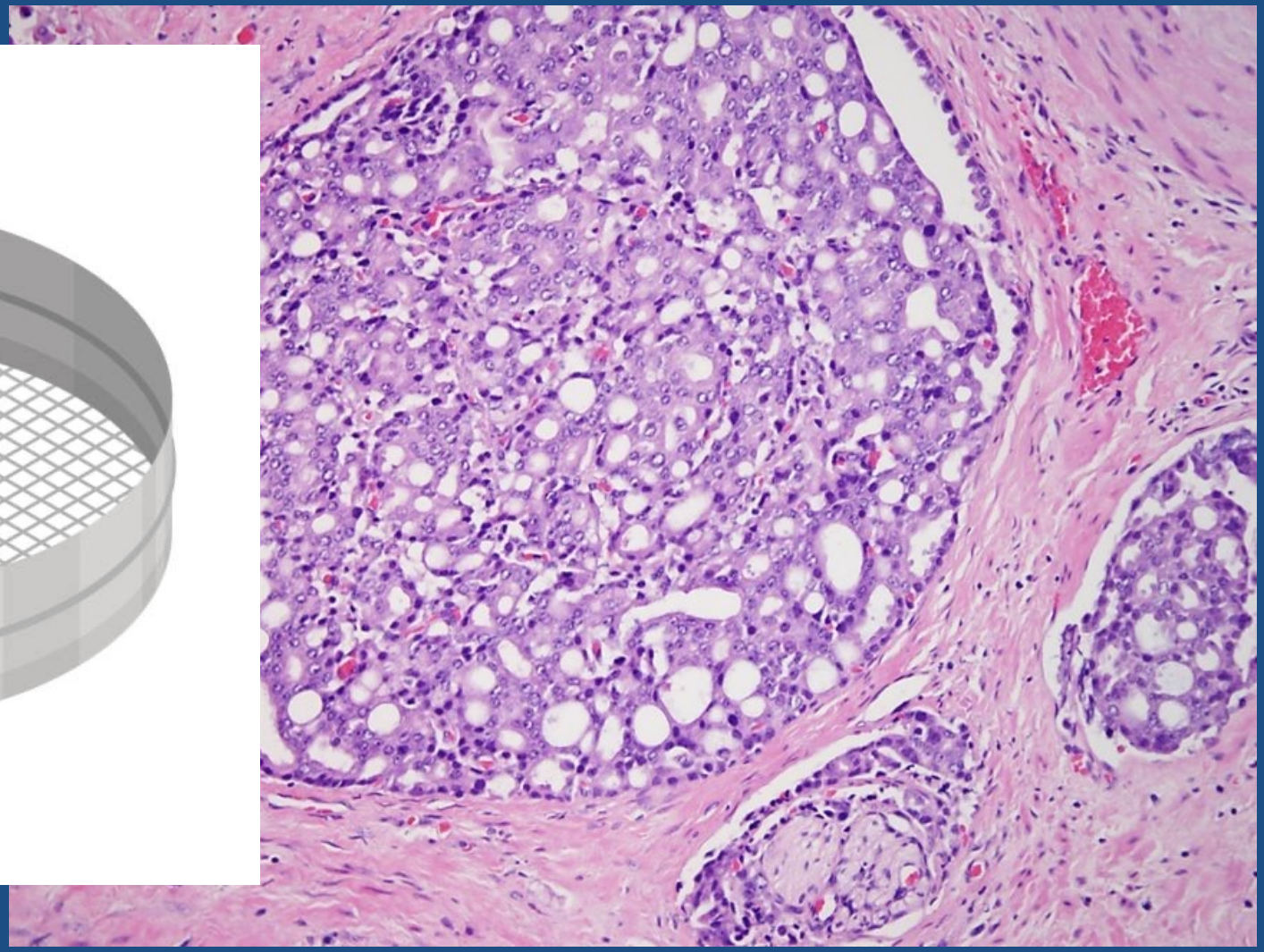


Grading prostate cancer

- Gleason p

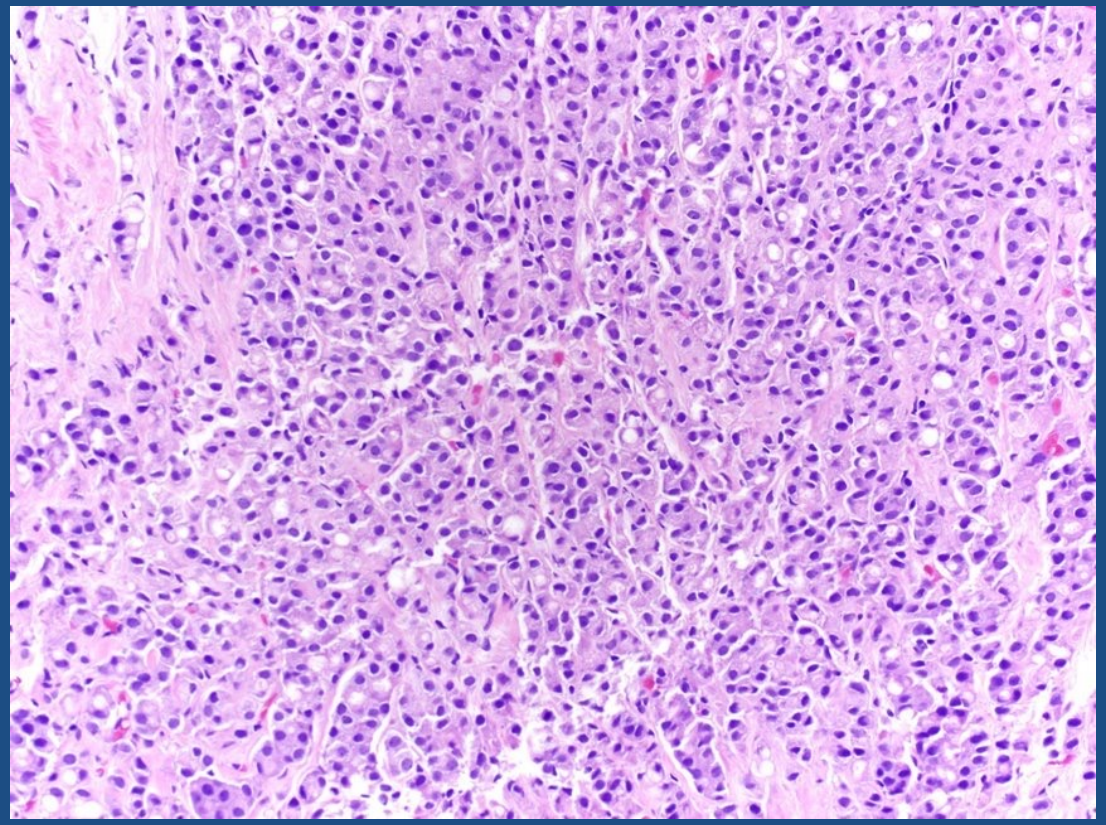
  - larg

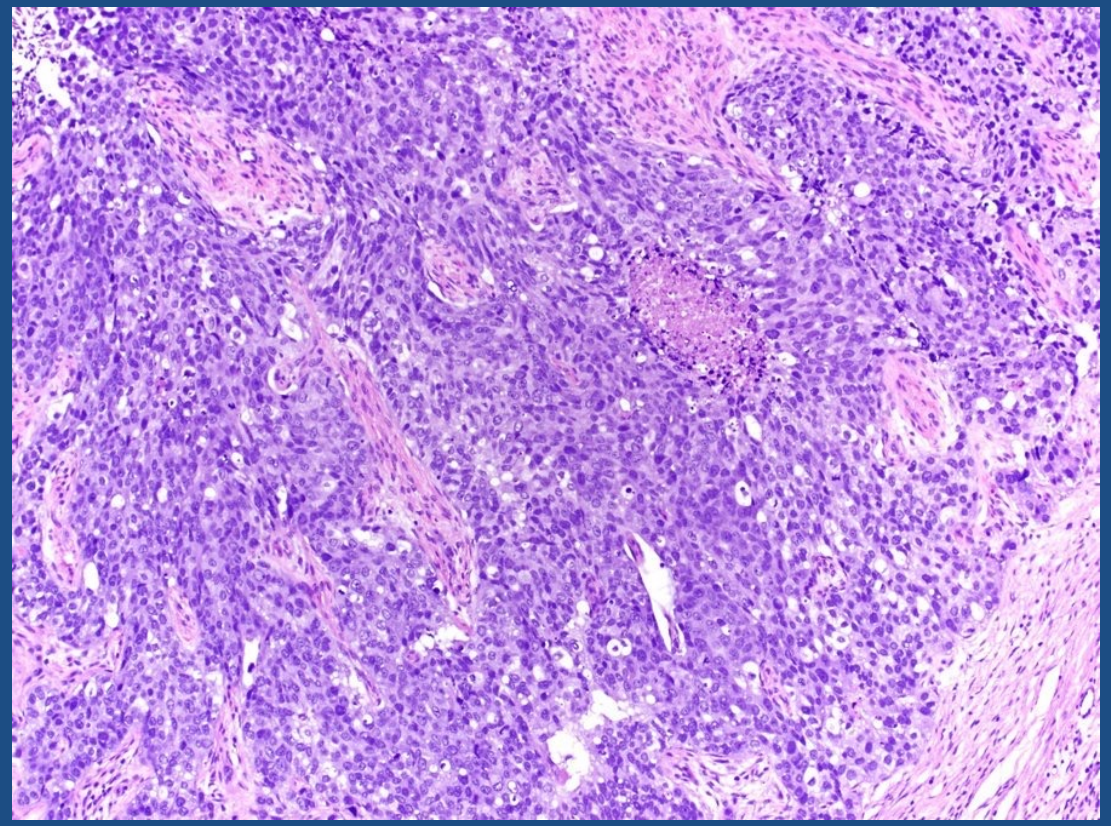




Grading prostate cancer

- Gleason pattern 5
  - No gland formation

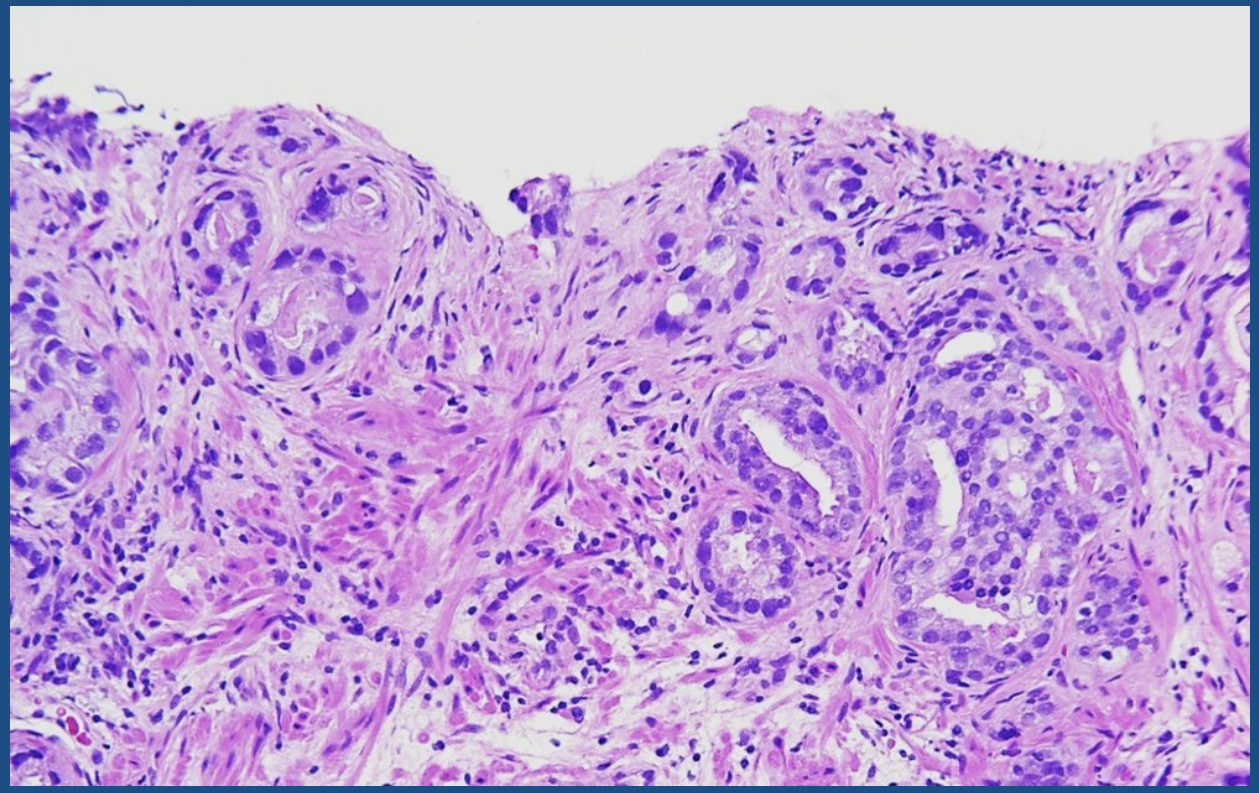




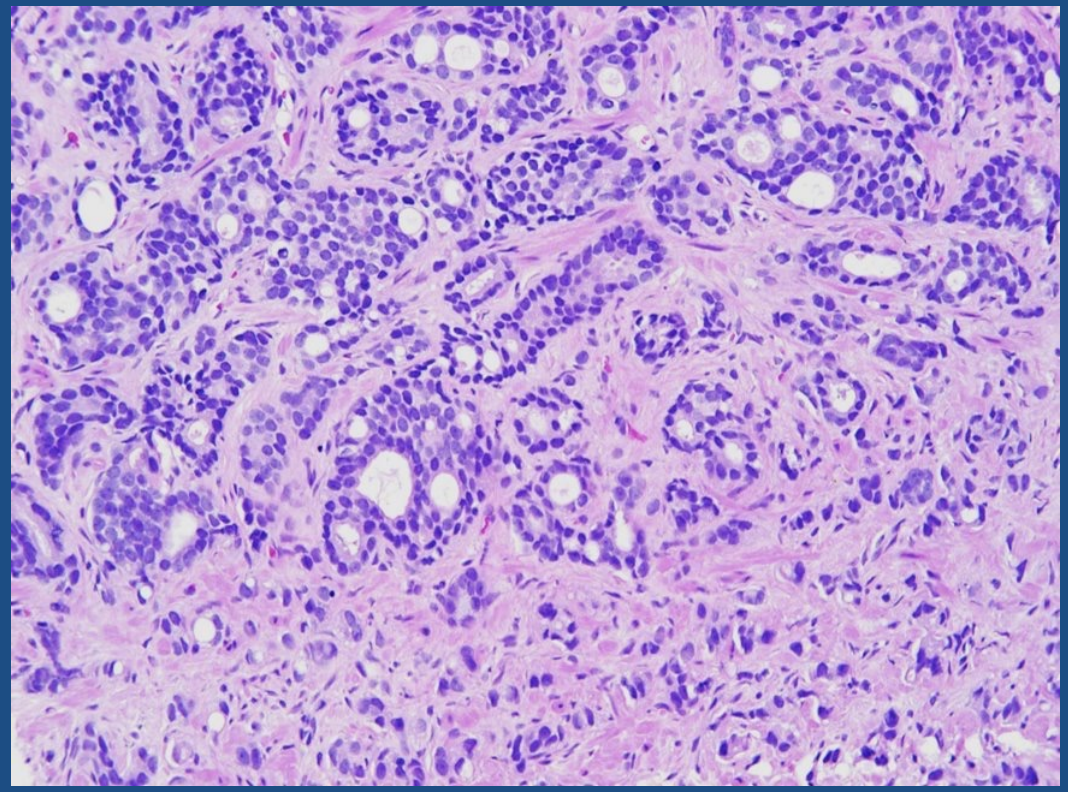
Single, individual cells and sheets of cells

How do we determine overall grade?

- Sum of two most common patterns



Gleason score 3+4=7



Gleason score 4+5=9

Grade Group System

- Primarily helps patients recognize that Gleason 6 is the "best" possible tumor to have and is not an intermediate grade cancer (as suggested by "6/10")

Grade group 1: Gleason score ≤6
Grade group 2: Gleason score 3 + 4 = 7
Grade group 3: Gleason score 4 + 3 = 7
Grade group 4: Gleason score 4 + 4 = 8, 3 + 5 = 8, 5 + 3 = 8
Grade group 5: Gleason scores 9–10

- Highlights difference in Gleason 7 disease

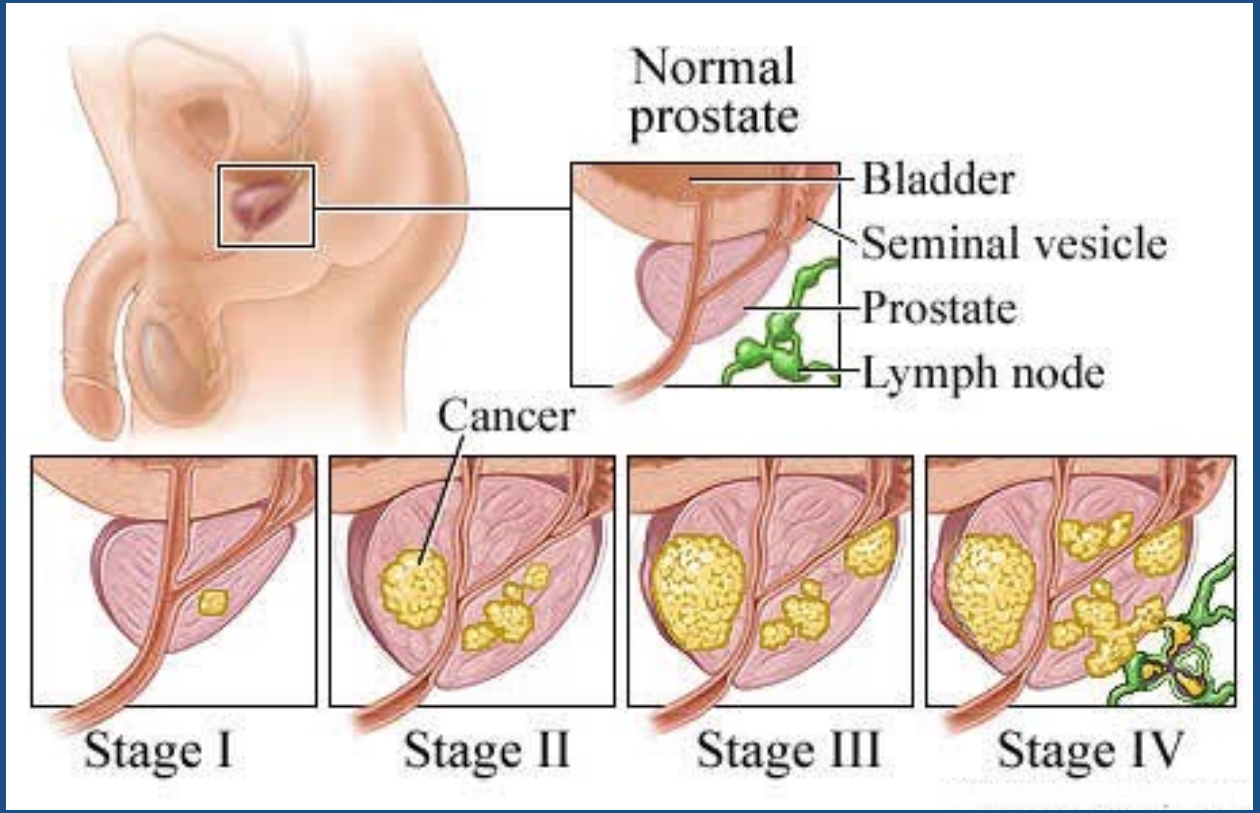
3+4=7 ≠ 4+3=7 (?!)

How does grading influence treatment?

- Active surveillance
- Radical Prostatectomy
- Radiation therapy
- +/- Hormone therapy (ADT)

Pathologists also determine prostate cancer stage

- Stage = extent of the cancer
- Also determines prognosis

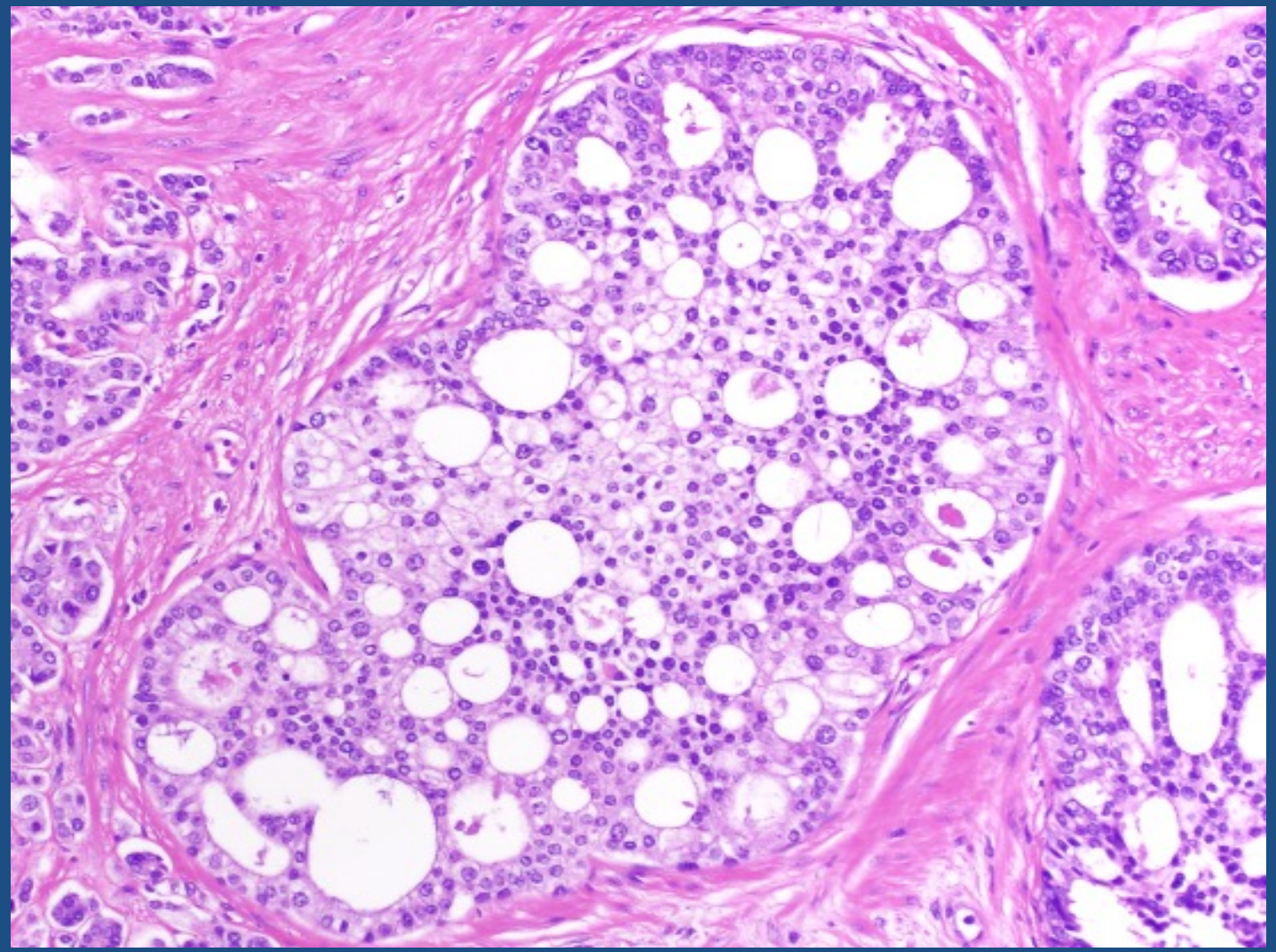


Other patterns pathologists see that can predict how prostate cancer may behave

Morphologies with prognostic significance:

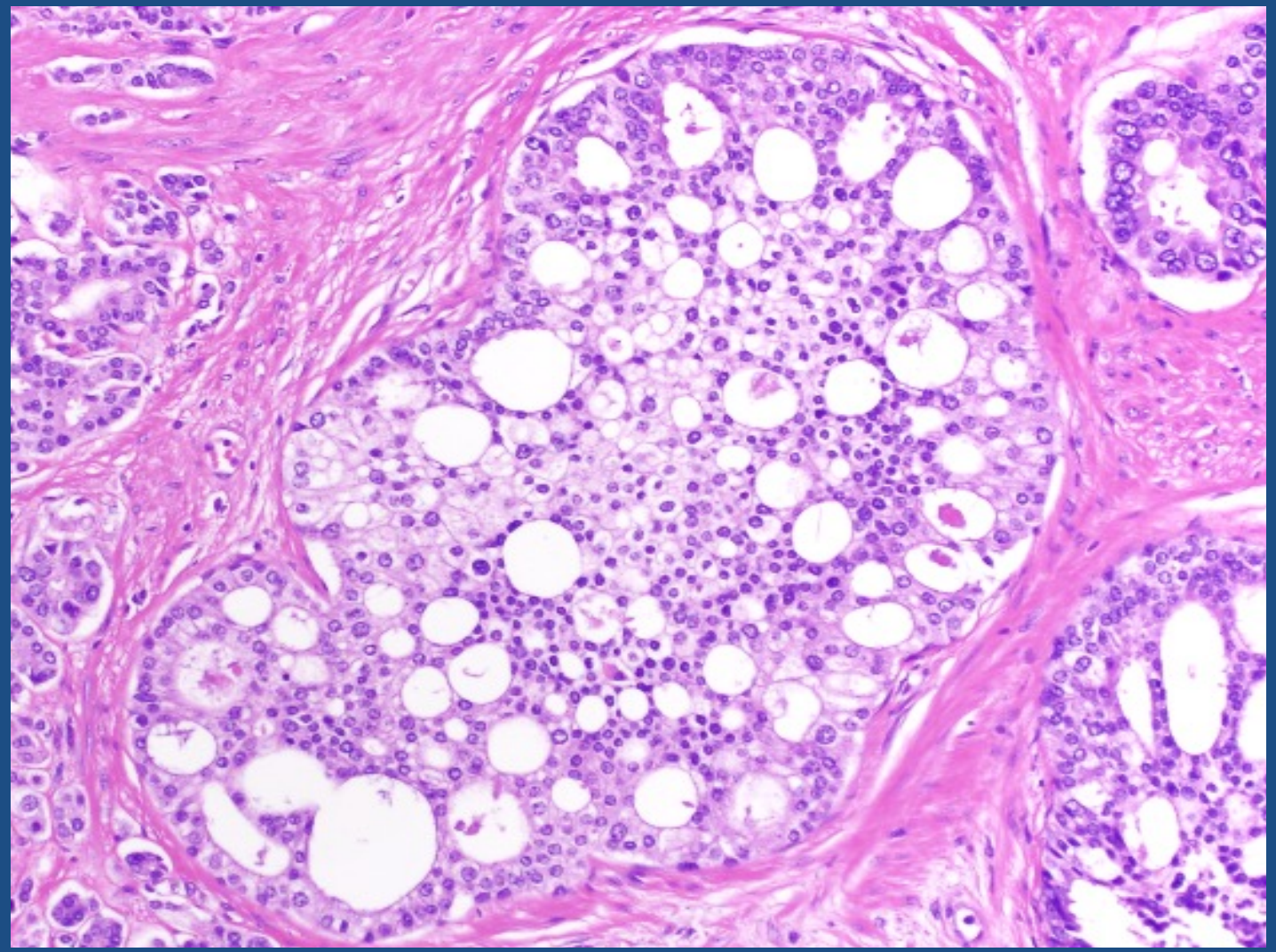
- Intraductal carcinoma of the prostate (“IDC-P”)
- Cribriform morphology

Intraductal carcinoma “IDC-P”



- Prostate cancer that grows within the ducts

Intraductal carcinoma “IDC-P”



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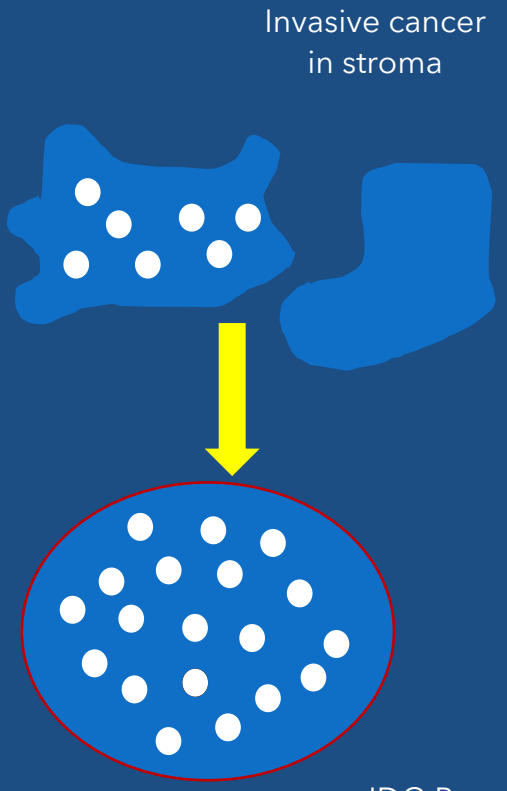

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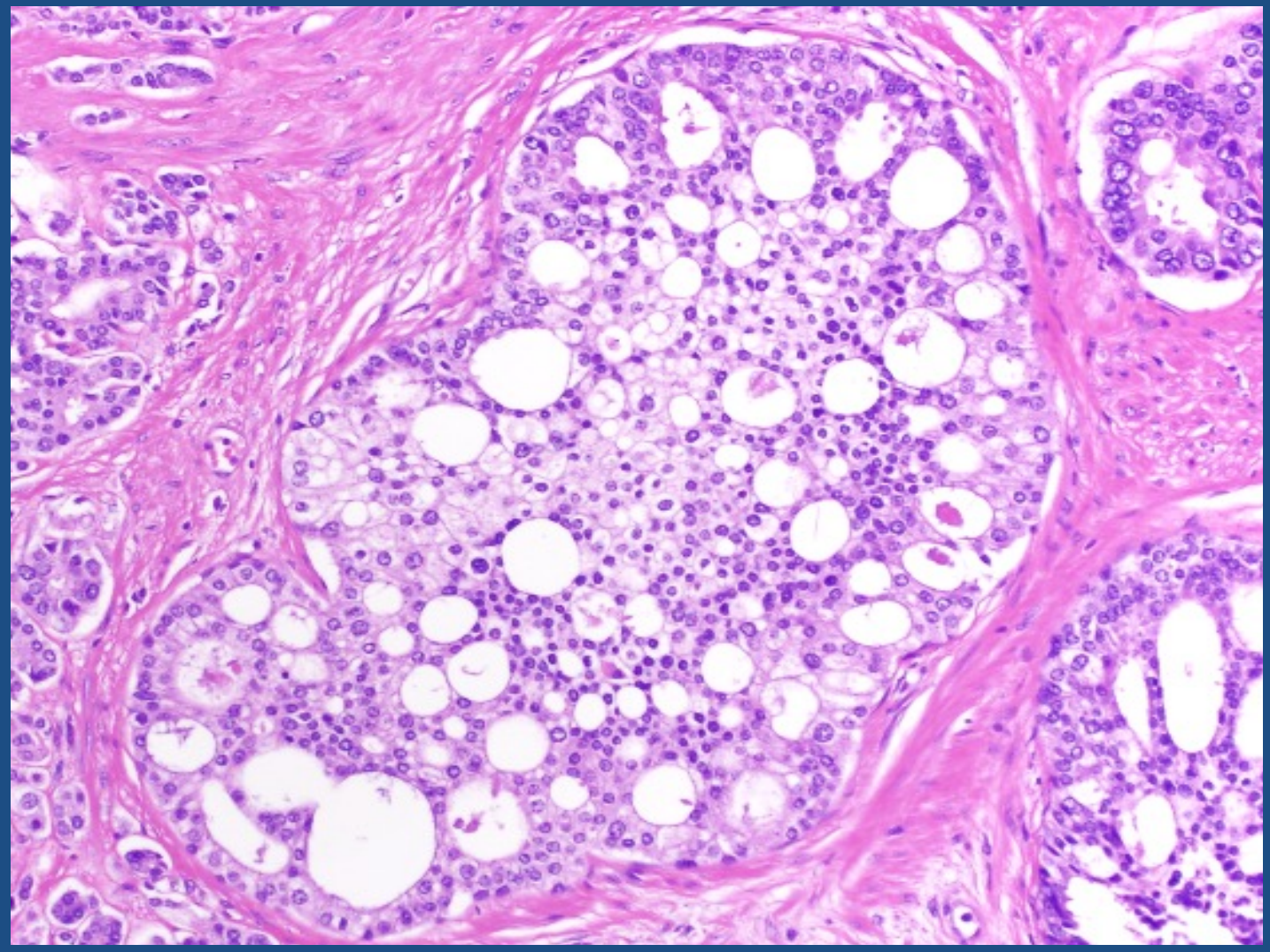
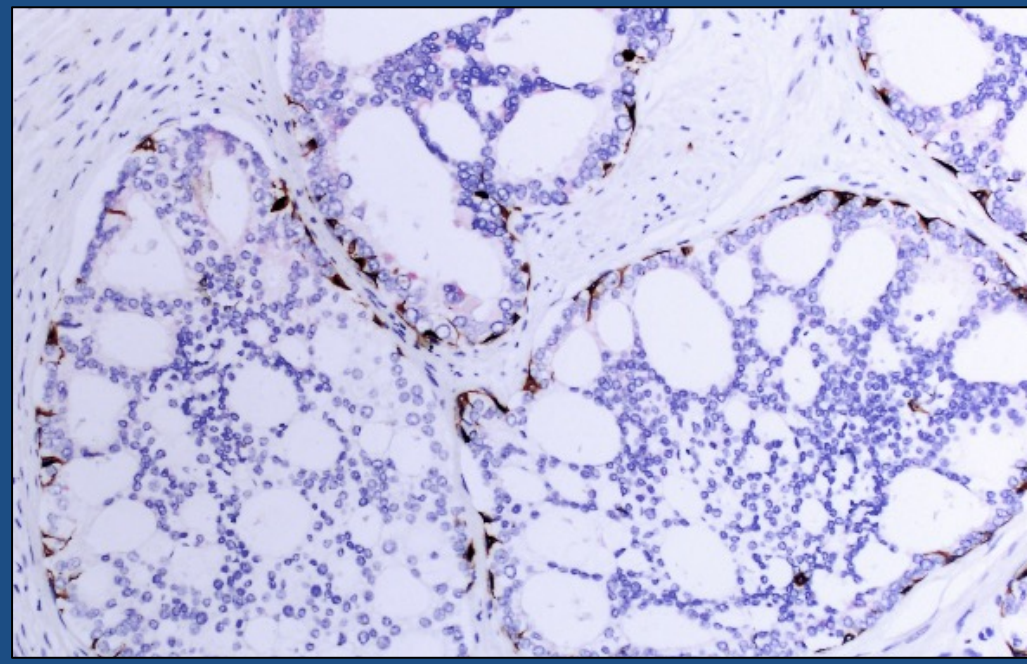
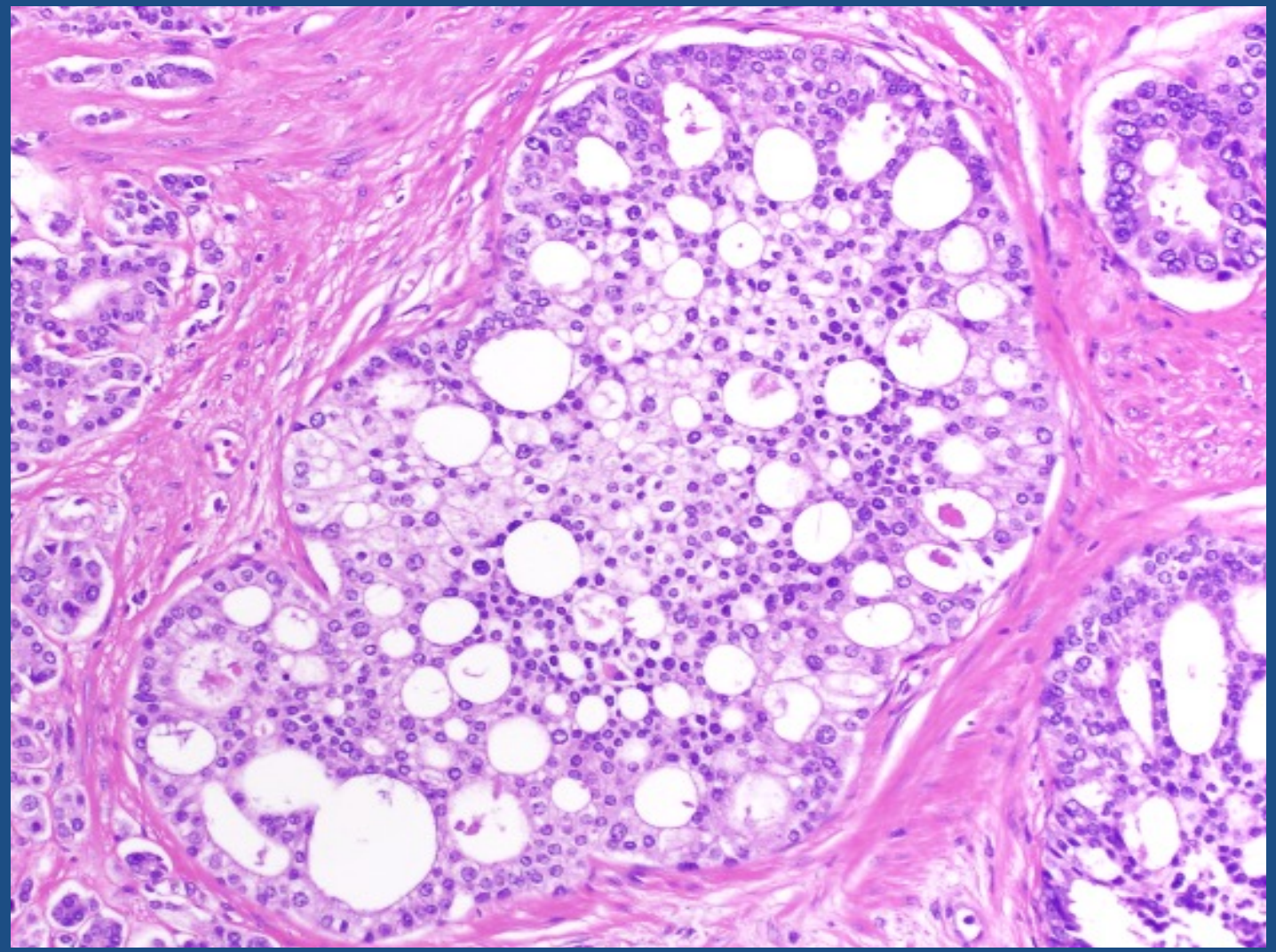
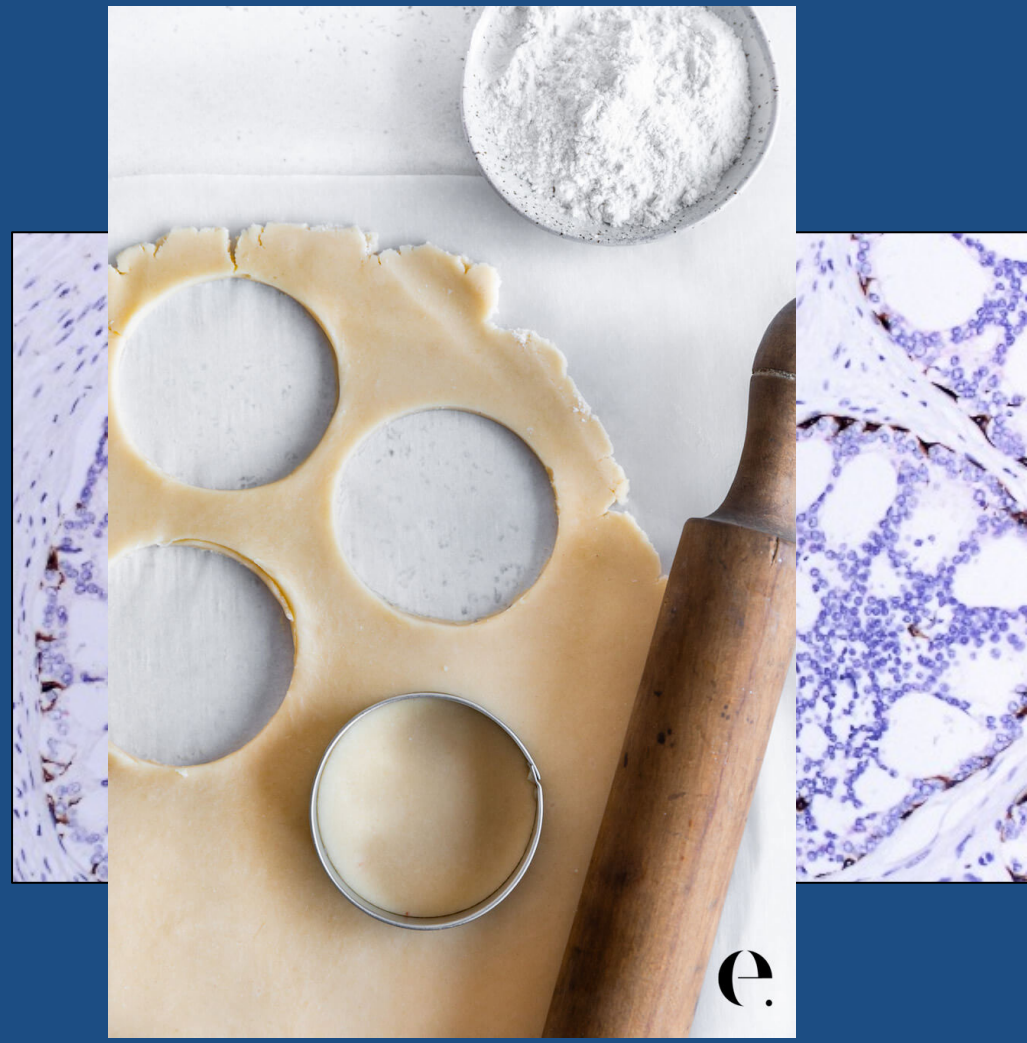




- Basal cells highlighted with brown stain

Intraductal carcinoma “IDC-P”



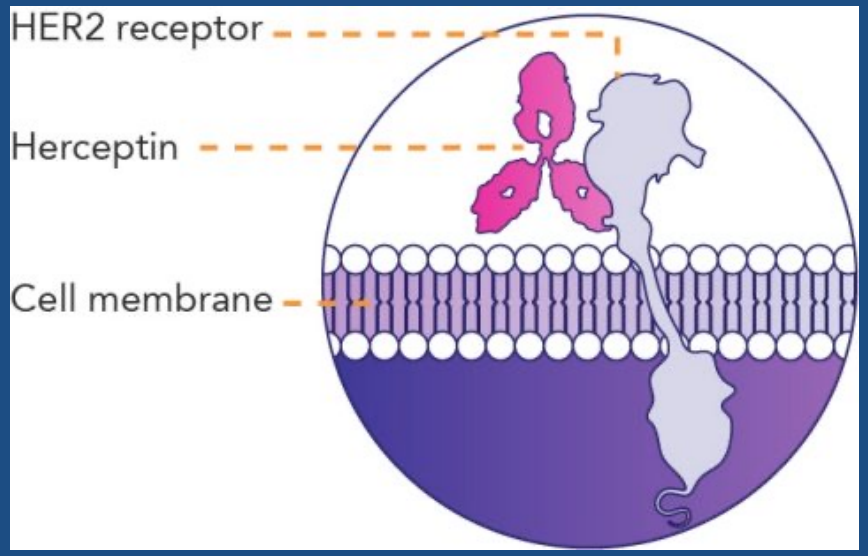


IDC-P and Cribriform Patterns Indicate Aggressive Prostate Cancer

- Information from pathologists helps urologists / oncologists determine the best course of treatment
- Even aggressive prostate cancers are highly treatable!
- Having more knowledge about how a cancer will behave helps doctors select the best treatment plan → individualized therapy

Ultimate Goal: Developing Therapies for Aggressive Cancers

- Example of a success story:
  - In breast cancer, tumors found to overexpress a specific protein (HER2) were very aggressive and had a worse prognosis
  - HER2 protein found to be targetable with a specific drug therapy (Herceptin)
  - Breast cancers showing HER2 overexpression now have a good prognosis since targeted drug therapy is highly effective



https://www.herceptin.com/

Similar Recent Advances in Prostate Cancer

- Inherited gene mutations in *BRCA1/BRCA2* associated with familial breast and prostate cancers
- Non-hereditary prostate cancers can develop mutations in these genes
- PARP inhibitors (previously used for breast and ovarian cancers) recently found to be effective therapies for prostate cancers that have these mutations

Let's return to IDC-P/cribriform morphology in prostate cancer…

- If we study the cells within these aggressive patterns, can we figure out what makes them aggressive biologically ?
- Can we identify new therapeutic targets?
- Can we develop new treatments tailored to these prostate cancers?

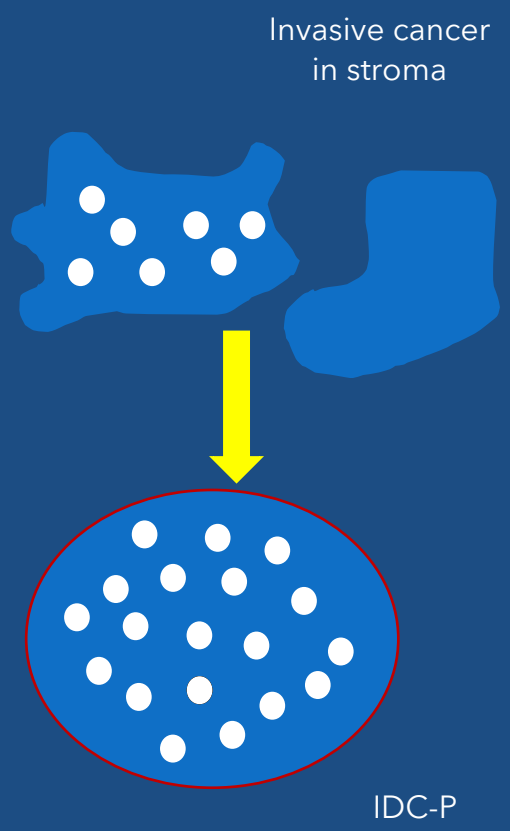
Recent research advances in IDC-P/cribriform prostate cancers

- Higher genomic instability (i.e. more genes are altered)
- Overexpression of a unique gene- *"Schlap1"*
- More hypoxia (i.e. oxygen deprivation)
- Express genes associated with metastasis (but also potential targets for therapies)- *JAG1/NOTCH*
- Lesser and altered immune response

Chua et al. *European Urology*. 2017 Nov;72(5):665-674

Wong HY et al. *Nature Communications*. 2022 Oct 13;13(1):6036.

Research I've Done on IDC-P



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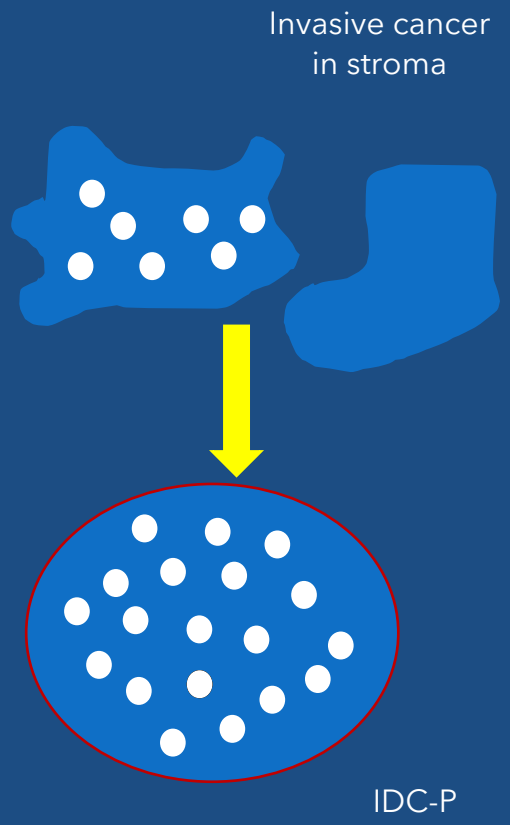

- Some prostate cancers showing IDC-P may begin within the ducts instead of re-entering them from the stroma

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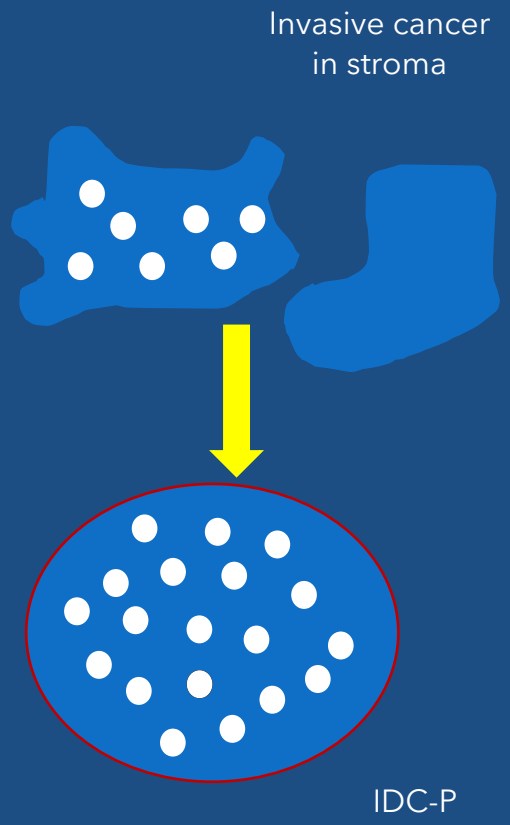

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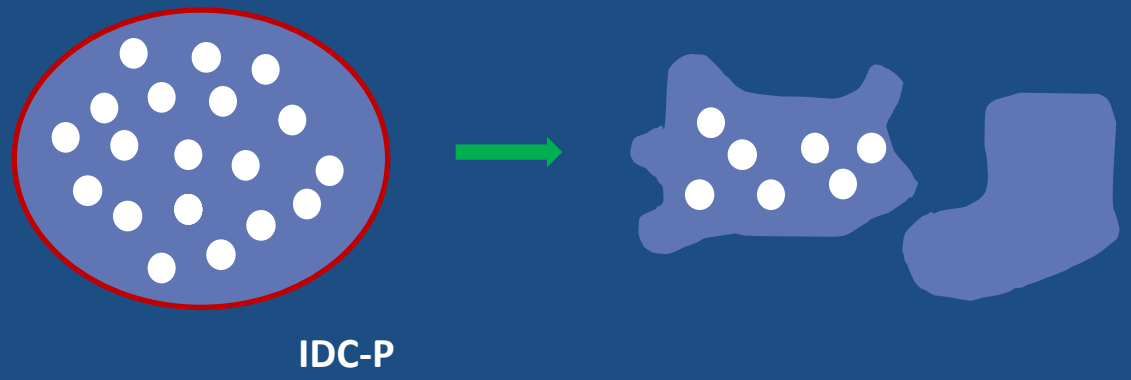

This Type of IDC-P Has Therapeutic Targets!

- We sequenced the DNA from this particular type of IDC-P
- Found mutations in genes in a particular molecular pathway (MAPK/PI3K) that are targetable with therapies used in other cancers
- MEK, RAS, RAF inhibitors used successfully in other cancers (melanoma, lung cancers, liver cancers)
  - A lot more work to be done!

Khani et al. *Journal of Pathology*. 2019 Sep;249(1):79-89

Take Home Points

- What pathologists see under the microscope has great importance for determining the best treatment for individual patients

- Grading of prostate cancer is highly nuanced and is one of the most important factors in selecting appropriate treatment

Take Home Points

- Pathologists report other patterns they see in cancer (e.g. cribriform, intraductal carcinoma) that indicate the aggressiveness of a tumor, further influencing therapy decisions

- Continuing to study these aggressive prostate cancer types will help us to develop new and more targeted therapies

    - Pathologists also play an important role in prostate cancer research!

The Pathologist's Crucial Role in Cancer Care

By Francesca Khani, MD

https://weillcornellgucancer.org/tag/dr-francesca-khani/

Questions?