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# WHAT YOU ARE NOT READING & NOBODY IS TEACHING YOU

## THE PATHOLOGY COMIC BOOK

70 high-yield panels — straight off the whiteboard, into your exam.

For FRCPATH Part 1, FRCPATH Part 2, NEET-SS Pathology & MD/DNB Pathology

FRCPATH Part 1

FRCPATH Part 2

NEET-SS Pathology

MD/DNB Pathology

*“Scroll AI content. Study from the OG master.”*

By Dr. Maitrayee Roy & Dr. Akshay Bali — eLearning FRCPATH

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# Before You Dive In...

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Somewhere between a whiteboard marker running dry and a 2 a.m. Instagram scroll, the eLearning FRCPATH team has been quietly building the pathology cheat sheet nobody handed you in med school. This book is that entire feed, rescued from your camera roll and put in an order that actually makes sense — bone leads into skin, lung leads into lymphoma, kidney leads into colon. Every panel keeps its original artwork exactly as posted. The little caption underneath is just us narrating — think of it as the sarcastic senior resident standing over your shoulder while you revise. Read it once for fun. Read it again for the marks.

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# Meet Your Instructors

The pathologists behind every whiteboard scrawl in this book.



## Dr. Maitrayee Roy

**MD FRCPath (Histopathology)**

Experienced pathologist with a demonstrated history of working in the hospital & health care industry. Skilled in Histopathology, Hematopathology, Chemical Pathology.

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## Dr. Akshay Bali

**MD DipRCPath (Histopathology)**

Experienced pathologist with a demonstrated history of working in the hospital & health care industry. Skilled in Histopathology, Hematopathology, Chemical Pathology.

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# 01

## BONE & SOFT TISSUE PATHOLOGY

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*The lesions that look alike under the scope until one marker ruins the disguise.*

8 panels • maps to:

FRCPATH Part 1

FRCPATH Part 2

**WHAT YOU ARE NOT READING  
& NOBODY IS TEACHING YOU**



# MDM2 SAVES THE DIAGNOSIS

In bone & soft tissue lesions, **morphology can be misleading**.  
MDM2 helps you make the right call.

## THE DIAGNOSTIC DILEMMA



Well-differentiated  
**liposarcoma** (WDLS)

vs.

Benign lipoma  
Atypical lipomatous tumor (ALT)



They look alike  
under the microscope!



## MDM2 TO THE RESCUE

- ✓ MDM2 gene amplification present in WDLS / ALT
- ✓ Detected by IHC or FISH
- ✓ Highly specific and diagnostically decisive



★ **POSITIVE MDM2 =**  
Think WDLS / ALT



When morphology is equivocal,  
don't guess. **DO THE TEST.**



One marker.  
One correct diagnosis.  
Big difference in patient care.



**TAKE-HOME MESSAGE:**  
MDM2 is not just a marker, it's a decision maker.



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WHAT YOU ARE **NOT** READING  
& **NOBODY** IS TEACHING YOU



# GIANT CELL TUMOR OF BONE (GCT) DENOSUMAB CHANGES EVERYTHING



**DENOSUMAB** (Anti-RANKL) → Blocks osteoclast formation

## BEFORE DENOSUMAB



**NUMEROUS  
OSTEOCLAST-TYPE  
GIANT CELLS**

The hallmark  
of GCT



## AFTER DENOSUMAB



**GIANT CELLS  
ALMOST  
DISAPPEAR**

This is the most  
important change!



### KEY TAKEAWAYS

- ✓ Denosumab blocks RANKL → osteoclasts (giant cells) disappear.
- ✓ Mononuclear stromal cells remain.
- ✓ New woven bone and fibrosis appear.



### DIAGNOSTIC PITFALL

Post-denosumab GCT can mimic low-grade osteosarcoma, fibrous dysplasia, or healing fracture.



### ALWAYS ASK:

Has the patient received denosumab?



**TAKE-HOME MESSAGE:** Denosumab doesn't kill the tumor, it only **changes how it looks.**



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*Plot twist: the drug doesn't kill the tumor. It just gives it a really convincing disguise. Don't fall for it.*

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# H3F3A MUTATION IS **NOT** UNIQUE TO GIANT CELL TUMOR



## COMMON MUTATION

**H3F3A G34W**

~90–95% of  
GCTs



## RARE MUTATIONS

**G34L** **G34M**

**G34R** **G34V**

Same codon,  
different amino acid



## WHY IT MATTERS

Antibody detects  
only G34W.

- ✗ G34L = negative
- ✗ G34M = negative
- ✗ G34R = negative

Still true GCTs!



## PRACTICAL EXAMPLE

Morphology classic  
but H3G34W stain

**NEGATIVE**

Could be non-W  
mutation.  
Confirm by  
sequencing.



**MORPHOLOGY + MOLECULAR TESTING =  
ACCURATE DIAGNOSIS**



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*One negative stain and half the class writes "not GCT" on the answer sheet. The other half keeps the marks.*

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**SERIES**

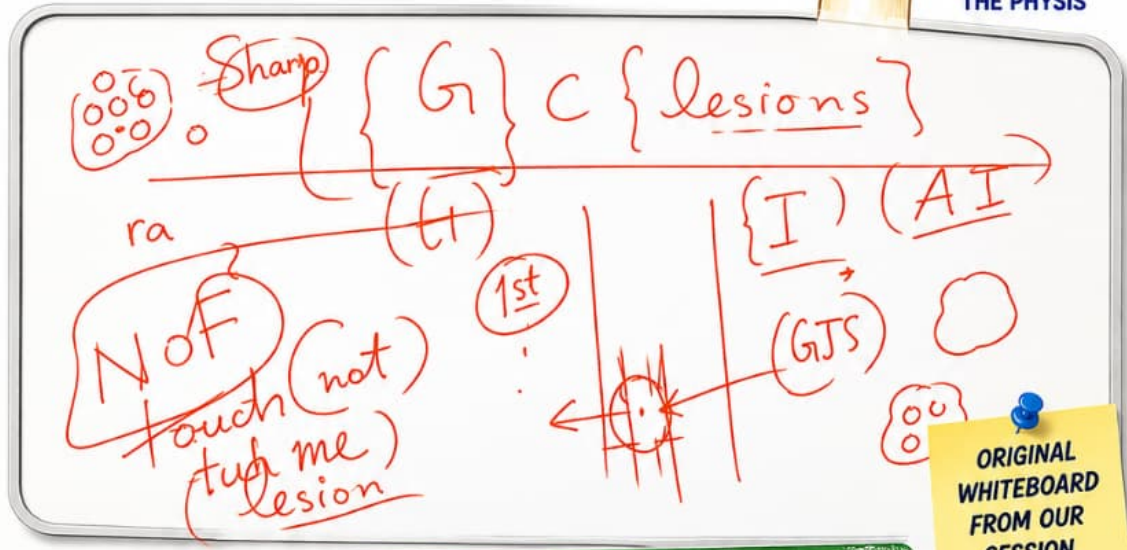
**NON-OSSIFYING  
FIBROMA (NOF)**

**FIBROUS CORTICAL DEFECT**





**ECCENTRIC  
METAPHYSEAL  
LESION  
ADJACENT TO  
THE PHYSIS**



**ORIGINAL  
WHITEBOARD  
FROM OUR  
SESSION**

**TOUCH-ME-NOT LESION**



It is most commonly diagnosed in  
the second decade of life (ages 10 to 15).



**TOUCH-ME-NOT  
LESION**

Incidental, asymptomatic  
finding in growing children.

**NO TREATMENT NEEDED!**



**RADIOLOGICAL  
FEATURES**

Well-defined, eccentric  
metaphyseal lytic lesion  
adjacent to the physis  
with sclerotic rim.



**HISTOPATHOLOGICAL  
PITFALL**

Histology can mimic  
GCT of bone.

**ALWAYS CORRELATE  
WITH RADIOLOGY.**

**REAL PATHOLOGY. REAL LEARNING. REAL CONFIDENCE.**

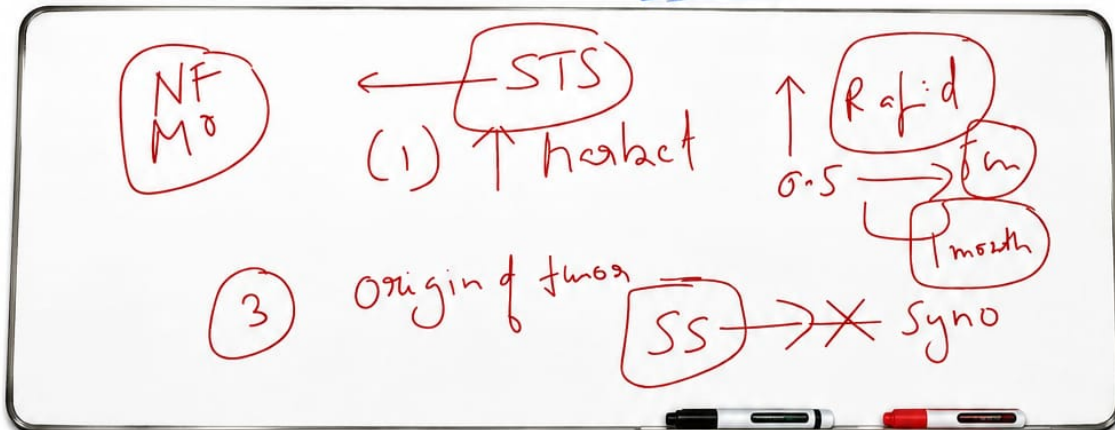
Also known as: the lesion your radiologist spots by accident and your report is happy to leave alone.

WHAT YOU ARE NOT READING &  
NOBODY IS TEACHING YOU

# 4 SOFT TISSUE TUMOR RULES THAT WILL FAIL YOU IN THE EXAM



What they teach **vs.** what actually happens.



1

## ATYPIA + MITOSIS ≠ MALIGNANCY



Benign entities like Nodular Fasciitis can show marked atypia & mitoses yet remain strictly benign.

2

## RAPID GROWTH ≠ MALIGNANCY



Benign soft tissue lesions can grow fast.  
Examples: Nodular Fasciitis, Myositis Ossificans.

3

## TUMOR NAME ≠ CELL OF ORIGIN



Names can mislead.  
Example: Synovial Sarcoma does not arise from synovial membranes or cells.

4

## SAME HISTOLOGY ≠ SAME TUMOR



Identical histology can belong to completely different entities. Use context, IHC, and molecular tools.



**RULES EXIST. EXCEPTIONS DEFINE EXPERTISE.**



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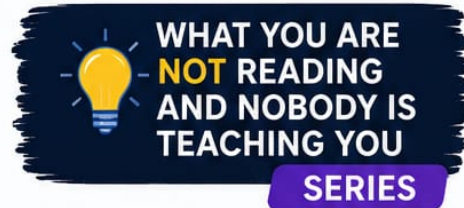
Scroll AI content. Study from the **OG** master.

Four things your textbook swears are always true. The exam has other ideas.



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# SATB2

THE DEVELOPMENTAL  
SIGNAL BEHIND ITS  
SURPRISING POSITIVITY

A MASTER REGULATOR OF **CRANIOFACIAL DEVELOPMENT**

## COMMON USES OF SATB2 (EVERYONE IS AWARE OF)



### 1. OSTEOBLASTIC / BONE TUMORS

- Osteosarcoma (especially osteoblastic)
- Osteoblastoma
- Osteoid osteoma



### 2. GASTROINTESTINAL ORIGIN TUMORS

- Colorectal adenocarcinoma (high sensitivity & specificity)
- Appendiceal adenocarcinoma

#### KEY TAKE-HOME (THE CLASSIC ONE)

SATB2 positivity strongly supports osteoblastic differentiation or colorectal / appendiceal origin.



## WHY SATB2 LIGHTS UP ODONTOGENIC TUMORS

SATB2 is essential for development of the **craniofacial skeleton** and **teeth**.



Neural crest cell differentiation



Osteoblast differentiation



Maxillary and mandibular development



Tooth morphogenesis



Odontogenic tumors arise from tissues participating in tooth development (odontogenic epithelium & ectomesenchyme).

They retain the embryonic transcriptional profile, including **SATB2** expression.



### SATB2 POSITIVITY = DEVELOPMENTAL MEMORY

Odontogenic tumors remember their embryonic roots. That's why **SATB2** shows up.



SCROLL AI CONTENT. STUDY FROM THE **OG MASTER**.

*SATB2 turning up in a jaw tumor is basically running into your dentist at the gym.*



WHAT YOU'RE **NOT READING**  
& NOBODY IS **TEACHING YOU**



# GLI1-ALTERED TUMORS VS SOLITARY FIBROUS TUMOR

|                    | GLI1-ALTERED TUMORS<br>(GLI1 amplification / GLI1 fusion) | SOLITARY FIBROUS TUMOR (SFT)                |
|--------------------|-----------------------------------------------------------|---------------------------------------------|
| GENETIC ALTERATION | GLI1 amplification or GLI1 fusion                         | NAB2::STAT6 gene fusion                     |
| CELL PATTERN       | Nested epithelioid or spindle cells                       | Patternless spindle cells                   |
| VASCULATURE        | Branching ("staghorn") vessels                            | Branching (hemangiopericytoma-like) vessels |
| STAT6 IMMUNOSTAIN  | STAT6 <b>NEGATIVE</b>                                     | STAT6 <b>NUCLEAR POSITIVE</b>               |



## 12q13-15: DIAGNOSTIC TRAP



GLI1  
12q13.3  
CDK4  
12q14.1  
MDM2  
12q15

Large 12q13-15 amplicon

Co-amplification of  
GLI1 + CDK4 + MDM2



MDM2 amplification can occur as part of the same 12q13-15 amplicon as GLI1. Not every MDM2-amplified tumor is dedifferentiated liposarcoma. Correlate morphology.



## PITFALL



MDM2 AMPLIFICATION  
≠ DEDIFFERENTIATED  
LIPOSARCOMA



Correlate morphology  
+ molecular findings.



THINK BEYOND MORPHOLOGY. THINK GLI1.



CONFIRM WITH RNA SEQUENCING OR FISH.



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*Two staghorn-vessel tumors walk into a lab. Only STAT6 knows which one's which.*

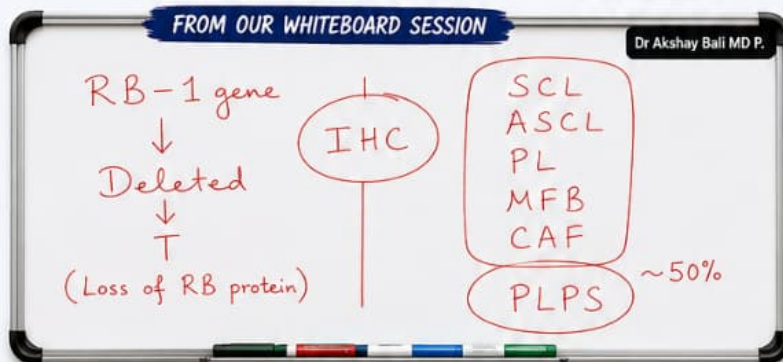
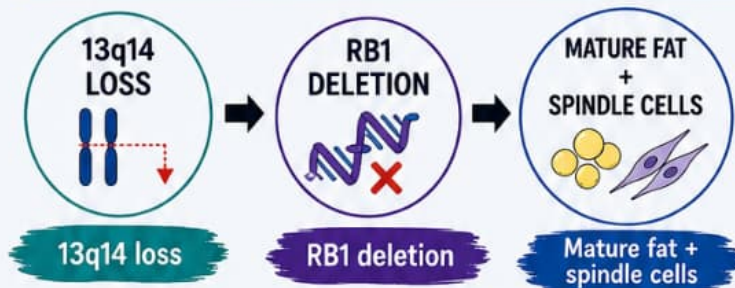
WHAT YOU ARE  
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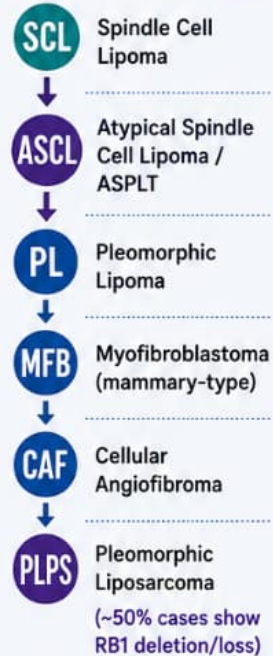
# RB1-DELETED

## SOFT TISSUE / MESENCHYMAL TUMORS

Different Diagnoses. Common Genetics. Common Morphologic Thread.



### THE SPECTRUM



WHO classifies tumors by molecular alterations.  
You should too.

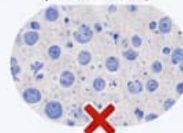


#### DIAGNOSTIC TOOL:

### Rb PROTEIN IHC

Loss of nuclear Rb expression in tumor cells (internal controls like endothelial cells retain staining)

TUMOR CELLS  
(Rb IHC LOSS)



INTERNAL CONTROL  
(ENDOTHELIAL CELLS)



**ONE GENETIC DRIVER.  
MULTIPLE DIAGNOSES.  
SHARED MORPHOLOGIC THREAD.**



**THINK GENETICS,  
NOT JUST MORPHOLOGY.**

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One gene deletion, six different names on the request form. RB1 really does get around.

# 02

## SKIN & MELANOCYTIC PATHOLOGY

---

*Melanoma, Spitz tumors, and the junctions that hold your skin together.*

4 panels • maps to:

FRCPATH Part 2

## Double Feature: Melanoma, Two Ways

**WHAT YOU ARE NOT READING AND NOBODY IS TEACHING YOU SERIES**

# MELANOMA BEYOND BRESLOW

KNOW THE DIFFERENCE. REPORT WITH CONFIDENCE.

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**MICROSATELLITISIS**

Microscopic

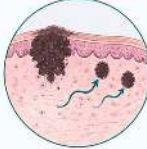
Microscopic separate nests



**SATELLITISIS**

Clinically visible

≤ 2 cm



**IN-TRANSIT METASTASIS**

Clinically or microscopically detectable

> 2 cm before regional lymph nodes

**KEY TAKEAWAY**

All three are regional spread via lymphatics. They matter for staging, prognosis & management.

Scroll AI content. Study from the OG master.

2cm doesn't sound like much until it's the line between a satellite and a metastasis.

**RECENT ADVANCES MD - FRCPath**

Real classroom → Real exam logic

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**MELANOMA TMB POWER**

MORE MUTATIONS. MORE NEOANTIGENS. STRONGER IMMUNITY.

- 1 UVB IMPACT**  
UVB → C>T  
Mutations drive TMB in skin.
- 2 HIGH TMB**  
Melanoma has an exceptionally high mutation burden.
- 3 NEOANTIGENS + TILs**  
More neoantigens → Recruit CD4+ & CD8+ T cells (TILs). More targets. Stronger response.
- 4 CHECKPOINT INHIBITORS WORK BETTER**  
TIL-rich microenvironment = Ideal for immune checkpoint inhibitors (ICIs).

**BRISK TIL = BETTER PROGNOSIS**

Higher TILs = Better Progression-Free Survival & Overall Survival.

**TILs in Primary Invasive Melanoma**

**BRISK** Lower risk of recurrence & mortality

**NON-BRISK** Intermediate risk

**ABSENT** Higher risk

Scroll AI content. Study from the OG master.

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Melanoma racks up more mutations than a first-year's differential list. For once, that's actually good news.

Two panels, one sun-damaged genome.



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# MOLECULAR CLASSIFICATION OF **SPITZ TUMORS**

THE **NEW ERA** IN DERMATOPATHOLOGY



The **WHO** adopted the concept of **MELANOCYTOMA** for lesions with **INTERMEDIATE BIOLOGICAL POTENTIAL** between **NEVUS** and **MELANOMA**.



## SPITZ MELANOCYTIC SPECTRUM



**SPITZ NEVUS**

Benign



**SPITZ MELANOCYTOMA**

Intermediate



**SPITZ MELANOMA**

Malignant



Spitz melanocytoma is **NOT** merely a diagnostic dilemma;  
it is recognized as an  
**INTERMEDIATE-GRADE MELANOCYTIC NEOPLASM**  
within the Spitz tumor spectrum.



**TODAY**  
**8:00 PM**  
— INDIA TIME —

**SKIN TUMORS**

FRCPATH Part 2 Preparation

**((•)) JOIN LIVE. STAY AHEAD.**



By Dr Maitrayee Roy, FRCPATH



**HIGH YIELD**  
Concepts



**EXAM FOCUSED**  
Approach



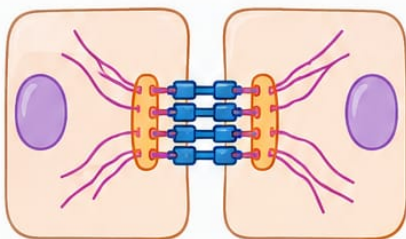
**RESULTS**  
DRIVEN

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*WHO finally admitted what every dermpath fellow already suspected: sometimes a Spitz lesion just won't pick a side.*

**STRONG BASICS****LEAD TO  
STRONG  
HISTOPATHOLOGY****DESMOSOMES**

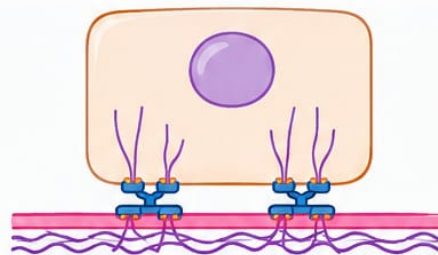
Cell to Cell Adhesion



- Links adjacent epithelial cells
- Provides mechanical strength
- Found **between** epithelial cells

**WHEN IT FAILS?****Pemphigus Vulgaris**

- ✓ Autoantibodies vs Desmoglein
- ✓ Desmosomes destroyed
- ✓ Loss of cell-to-cell adhesion (Acantholysis)
- ✓ Intraepidermal (suprabasal) blister
- ✓ Positive Nikolsky sign

**VS****HEMIDESMOSOMES**Cell to **Basement Membrane** Adhesion

- Anchors cells to **basement membrane**
- Maintains tissue **stability**
- Found at **basal surface**

**WHEN IT FAILS?****Bullous Pemphigoid**

- ✓ Autoantibodies vs BP180 (Collagen XVII) and BP230
- ✓ Hemidesmosomes disrupted
- ✓ Epidermis separates from basement membrane
- ✓ Subepidermal blister
- ✓ **Negative Nikolsky sign**

**DESMO** = **DUO** (Two cells together)**HEMI** = **HALF** (One cell attached to basement membrane)**STRONG BASICS. CLEAR CONCEPTS. CONFIDENT PATHOLOGIST.**

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*Desmo means duo, hemi means half. Mix that up on exam day and you'll have a blister of your own.*

# 03

## HEMATOLYMPHOID PATHOLOGY

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*Reed-Sternberg cells, popcorn cells, and the markers that tell them apart.*

4 panels • maps to:

FRCPATH Part 1

FRCPATH Part 2

TM

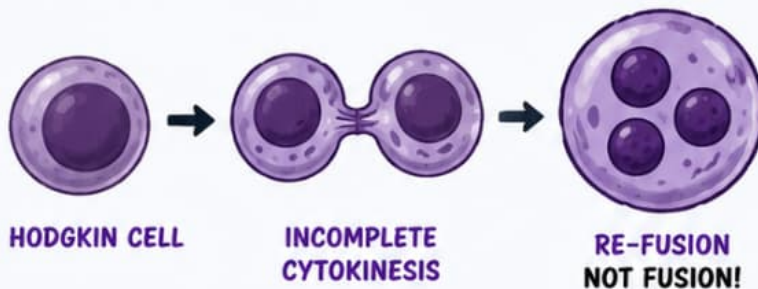


# WHAT YOU ARE NOT READING

## AND NOBODY IS TEACHING YOU

### SERIES

#### HOW REED-STERNBERG CELLS ARE BORN



RS CELLS FORM BY INCOMPLETE CYTOKINESIS & RE-FUSION OF DAUGHTER HODGKIN CELLS. NOT BY FUSION OF TWO INDEPENDENT NEOPLASTIC CELLS.

#### A CRIPPLED B-CELL THAT CHEATED DEATH

A transforming event—often driven by EBV infection or NF-κB pathway mutations—rescues the cell from death and turns it cancerous.



#### LINEAGE INFIDELITY: GLOBAL LOSS OF B-CELL IDENTITY



#### RS CELLS:

- ✗ LOSE CD19 & CD20
- ✗ LOSE IMMUNOGLOBULINS
- ✗ SHUT DOWN B-CELL MASTERS (E2A, PU.1, OCT-2)

BEYOND THE TEXTBOOK. BEYOND THE ORDINARY. **STUDY THE REALITY.**

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Reed-Sternberg cells aren't a merger of two cells. It's one cell that tried to divide, gave up halfway, and got famous anyway.



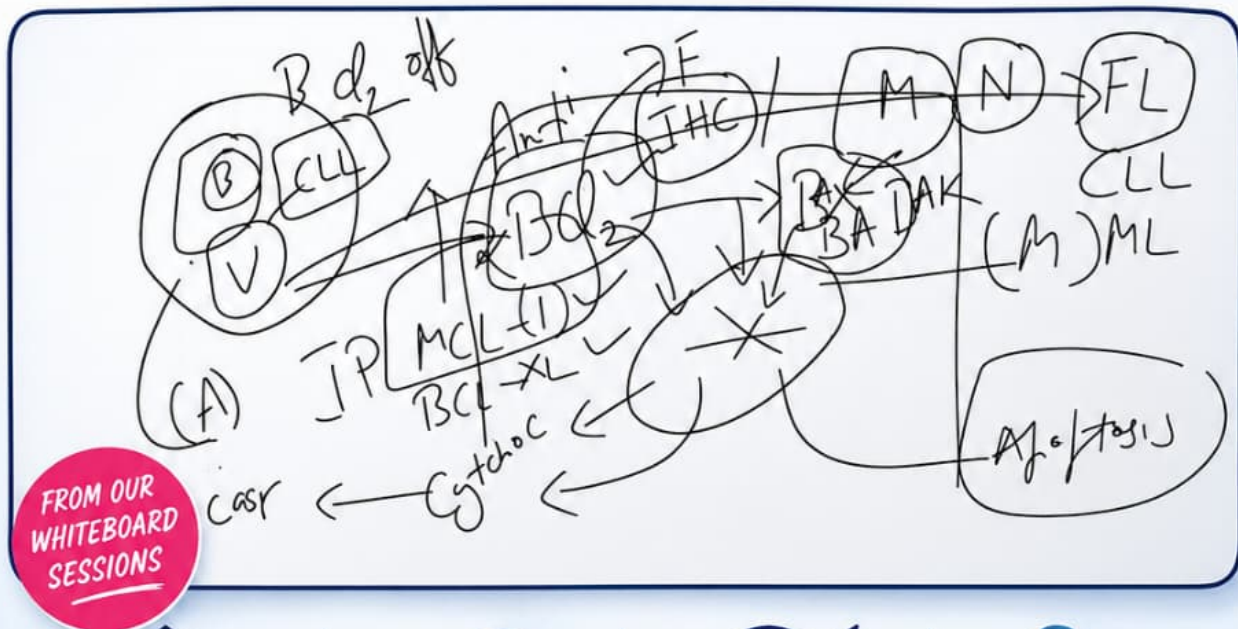
# WHAT YOU ARE **NOT** READING

≡ & NOBODY IS TEACHING YOU ≡

**BCL-2 IS NOT JUST A MARKER.**



IT'S A **SURVIVAL SWITCH.**



## BCL-2: THE GUARDIAN

Anti-apoptotic protein  
that protects B cells  
from death.



## WHEN BCL-2 IS OFF

BAX/BAK activate  
→ Cytochrome c release  
→ Caspases ON  
→ Cell dies.



## OVEREXPRESSED IN

- Follicular Lymphoma
- CLL
- Marginal Zone Lymphoma



## TARGET & RESISTANCE

- Venetoclax blocks BCL-2 (works in CLL)
- FL resists by switching to MCL-1 / BCL-XL



**REMEMBER THE ROLE, NOT JUST THE MARKER.**



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BCL-2 isn't on that report for decoration. It's the actual reason the cell refuses to die on schedule.



# WHAT YOU ARE **NOT** READING

**AND NOBODY  
IS TEACHING YOU**

**SERIES**




Smart Pathology Learning

## TRBC1 TESTING

(T-Cell Receptor Beta Constant 1)  
THE T-CELL EQUIVALENT OF  
**KAPPA/LAMBDA**  
IN **B-CELL** LYMPHOMAS



**B-CELL LYMPHOMA**  
Check  
KAPPA/LAMBDA  
Light Chain  
Restriction

≈



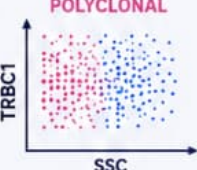
**T-CELL LYMPHOMA**  
Check  
**TRBC1**  
Restriction

### FLOW CYTOMETRY

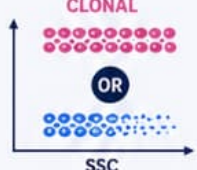


Fast, **low-cost**  
screening on  
viable cells

**POLYCLONAL**



**CLONAL**



**OR**





Uniform population all +  
or all - for **TRBC1** =  
**clonal restriction**

### IMMUNOHISTOCHEMISTRY (IHC)



**TRBC1 IHC** on  
FFPE tissue  
samples

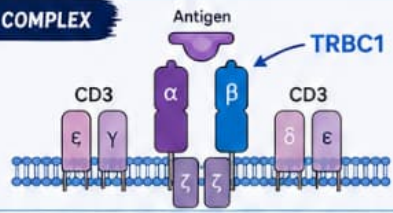




Essential for solid tissue  
biopsies where viable cells  
for flow cytometry are  
**unavailable**.

### T-CELL RECEPTOR (TCR) COMPLEX

**TRBC1** is the  
constant region of  
the **beta chain** of  
the T-cell receptor.



Helps determine  
if a T-cell  
lymphoid proliferation  
is **clonal (neoplastic)**  
or **reactive**.



**ONE MARKER. TWO POWERFUL METHODS. ONE DIAGNOSIS CLOSER.**

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*T cells finally got their own version of kappa/lambda. Took long enough.*

TM



# NLPHL IS A MISNOMER!

THE TRUTH BEHIND THE NAME



**NODULAR  
LYMPHOCYTE-  
PREDOMINANT  
B-CELL LYMPHOMA**

An indolent  
mature B-cell lymphoma.

**LP ("POPCORN") CELLS  
RETAIN B-CELL PROGRAM**



CD20



PAX5



OCT2

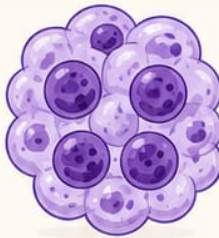


BOB1

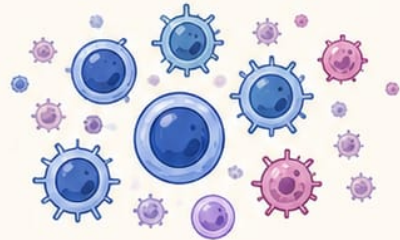
Unlike Reed–Sternberg cells  
of classical Hodgkin lymphoma.

**ITS DEADLIER BROTHER**

**T-CELL/HISTIOCYTE-  
RICH LARGE B-CELL  
LYMPHOMA**



**VS**



**IN BOTH,  
THE MALIGNANT CELLS ARE FEW.**



SEA OF REACTIVE  
NON-NEOPLASTIC  
CELLS



TUMOUR CELLS  
HIDE IN  
PLAIN SIGHT



“ THE CELLS THAT GRAB YOUR ATTENTION  
ARE OFTEN **NOT** THE TUMOUR. ”

THE TUMOUR IS THE CELL  
YOU'RE **STRUGGLING TO FIND.** ”

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BEYOND MEMORIZATION.

BEYOND TEXTBOOKS.

STUDY THE REAL BIOLOGY.

The actual tumour cells are the ones you can barely find in a sea of reactive lymphocytes. Typical.

# 04

## THORACIC & LUNG PATHOLOGY

---

*PD-L1, liquid biopsy, and every molecular subtype the lung throws at you.*

8 panels • maps to:

FRCPATH Part 1

FRCPATH Part 2

MD/DNB Pathology



WHAT YOU ARE **NOT** READING  
AND **NOBODY** IS TEACHING YOU

# WHY MESOTHELIAL CELLS STAND OUT

## THE MESODERMAL PARADOX

HYBRID  
BY NATURE.  
DEADLY BY  
CHOICE.



### NEVER FULLY "COMMIT"

Develop from mesoderm.  
Retain a hybrid state—  
neither fully epithelial  
nor mesenchymal.  
Always ready to switch  
(partial EMT).



### BAP1 SYNDROME

Germline BAP1 mutation  
predisposes to  
mesothelioma.  
Loss of BAP1 removes  
brakes on the hybrid state,  
fueling tumorigenesis.



### MESOTHELIOMA TRAIT

Asbestos + mutation  
unlocks innate flexibility.  
Biphasic tumors =  
epithelial clusters +  
aggressive spindle cells  
in one mass.

### BIPHASIC POTENTIAL

Epithelioid (gland-like)  
Sarcomatoid (spindle-shaped)  
or Biphasic (deadly mix).

ALL FROM ONE ORIGIN.



### WHERE IT STRIKES



**PLEURAL** ~75–90%  
Arises in the lining of the lungs (chest).



**PERITONEAL** ~6–20%  
Arises in the lining of the abdomen.



**PERICARDIAL** <1%  
From the sac surrounding the heart.



**TUNICA VAGINALIS** <0.5%  
From the pouch around the testicle.

### THE SILENT EXPOSURE



**WORKER**  
Asbestos dust  
on clothes  
& hair



**LAUNDRY  
VECTOR**  
Wives & daughters  
face concentrated  
exposure



**ABDOMINAL  
DIFFERENCE**  
Women → higher  
risk of peritoneal  
mesothelioma  
(swallowed fibers)

“ HIDDEN HISTORY.  
REAL CONSEQUENCES. ”



SESSION ON  
**LUNG TUMORS**



TODAY  
**6 PM**  
INDIA TIME



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SCROLL AI CONTENT. STUDY FROM THE **OG MASTER.**

Mesothelial cells can't fully commit to being epithelial or mesenchymal. Honestly, relatable.



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# WHAT YOU ARE **NOT** READING & NOBODY IS TEACHING YOU!



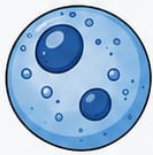
## IMA (Invasive Mucinous Carcinoma) of Lung

It's **Not** Just Another Adenocarcinoma

### 1 DIFFERENT LINEAGE

#### Typical Lung Adenoca

Type II Pneumocyte /  
Club Cell



Makes surfactant  
(TTF-1+, Napsin A+)



#### IMA

Goblet Cell  
(GI-type)



Makes mucin  
(TTF-1-, Napsin A-)

### 2 WHY STAINS TURN NEGATIVE

#### TTF-1

Master switch for  
lung identity



IMA switches it OFF!

#### Napsin A

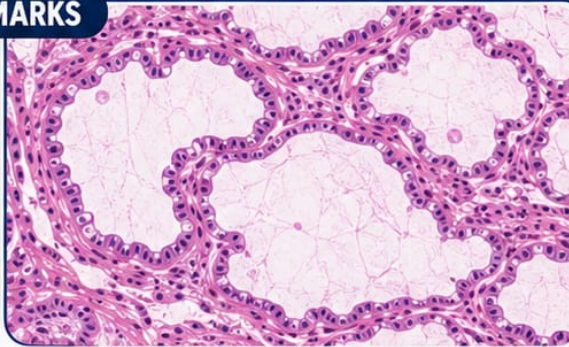
Needed for  
surfactant (Type II cells)



IMA makes mucin,  
not surfactant!

### 3 HISTO HALLMARKS

- ✓ Basal, uniform nuclei
- ✓ Pale mucin-filled cytoplasm
- ✓ Mucin pools in alveoli
- ✓ Looks like pneumonia on scans!



### 4 ENTERIC FEATURES



HNF4α



CK20  
(Patchy)



CDX2  
(Patchy)

**CK7 POSITIVE**  
RULE OUT GI PRIMARY  
VIA IMAGING

SCROLL AI CONTENT.  
STUDY FROM THE  
**OG MASTER.**

**IMA = GOBLET CELL DIFFERENTIATION**  
**NOT JUST A VARIANT, IT'S A DIFFERENT IDENTITY!**



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*Looks like pneumonia on the CT, behaves like a goblet cell under the scope. Lung adenocarcinoma having an identity crisis.*



# GET OVER PD-L1

**PD-L1 ALONE  
DOES NOT DECIDE  
ICI THERAPY.**

## 1 PD-L1 IS NO LONGER THE WHOLE STORY

- PD-L1 IHC alone is an imperfect predictive biomarker.
- PD-L1-high tumors can fail, PD-L1-negative can respond.

Current research integrates:



TMB



TILs



Gene-expression signatures



ctDNA



Spatial immune profiling



AI-based digital pathology

→ Better prediction of benefit

## 2 PERIOPERATIVE IMMUNOTHERAPY IS CHANGING CURE RATES

PD-1 inhibitors are now used:

**BEFORE SURGERY**  
(Neoadjuvant)

**AFTER SURGERY**  
(Adjuvant)

Significantly improved event-free survival in:



NSCLC



Melanoma



Bladder Cancer



Renal Cell Carcinoma

## 3 COMBINATION THERAPY IS THE FUTURE

Beyond PD-1 blockade alone



PD-1 + CTLA-4



PD-1 + VEGF inhibitors



PD-1 + Antibody-Drug Conjugates (ADCs)



PD-1 + Chemotherapy



PD-1 + Radiotherapy



PD-1 + STING agonists

→ Superior outcomes in selected patients

## 4 AI IS TRANSFORMING PD-L1 INTERPRETATION



- ✓ Improves PD-L1 scoring reproducibility
- ✓ Quantifies immune-cell distribution
- ✓ Predicts immunotherapy response from H&E in some studies
- ✓ Reduces interobserver variability

## 5 NEW IMMUNE CHECKPOINTS ARE EMERGING

PD-1 is no longer the only checkpoint. New targets include:



LAG-3



TIGIT



TIM-3



VISTA



B7-H3



Especially important for patients resistant to PD-1 therapy.



BEYOND PD-L1. TOWARDS **PRECISION.**

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*PD-L1 used to be the whole answer. Now it barely gets half the marks.*

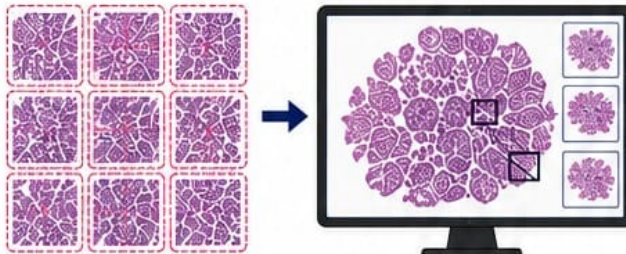


# eLEARNING FRCPATH™

Recent advances for MD exam

## STITCHING (TILE SCANNING)

Captures multiple overlapping tiles and stitches them to create the whole slide image.



Multiple overlapping tiles captured

Stitched whole slide image



Stop-and-go stage movement



Requires complex stitching algorithms



Relatively slower

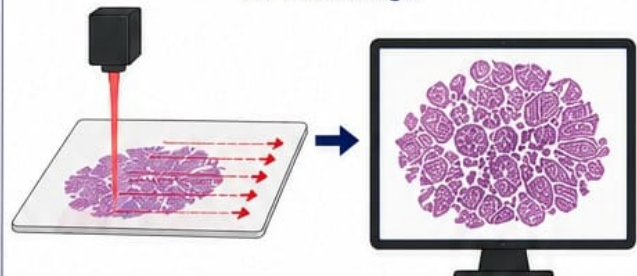


Stitching artifacts possible

VS

## LINE SCANNING

Captures the slide line by line with continuous movement to build the whole image.



Line by line capture with continuous movement

Assembled whole slide image



Continuous stage movement



Minimal stitching; line alignment



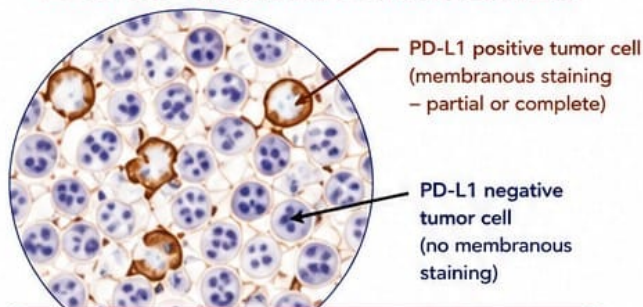
Generally faster



Line/banding artifacts possible

## PD-L1 TPS IN NSCLC

### PD-L1 IHC – INDIVIDUAL CELL ASSESSMENT



$$\text{TPS} = \frac{\text{PD-L1 positive viable tumor cells (with membranous staining)}}{\text{Total viable tumor cells}} \times 100$$



Only viable tumor cells counted



Partial or complete membranous staining



Immune cells, necrosis & cytoplasmic staining not included



Staining intensity (weak, moderate, strong) **DOES NOT** affect TPS. Any membranous staining at any intensity is considered positive.

### KEY CUTOFFS & SIGNIFICANCE

< 1%

#### Negative

Not eligible for PD-1 inhibitor monotherapy based on PD-L1 expression alone.

1–49%

#### Low PD-L1 expression

May be eligible for immunotherapy, often in combination with chemotherapy.

≥ 50%

#### High PD-L1 expression

Eligible for PD-1/PD-L1 inhibitor monotherapy in appropriate advanced NSCLC (no targetable driver mutations).



**TPS ≥ 50% = High PD-L1 expression**  
→ Eligible for PD-1/PD-L1 inhibitor monotherapy in NSCLC

Two ways to turn a glass slide digital, and one very specific cutoff the exam always circles back to.

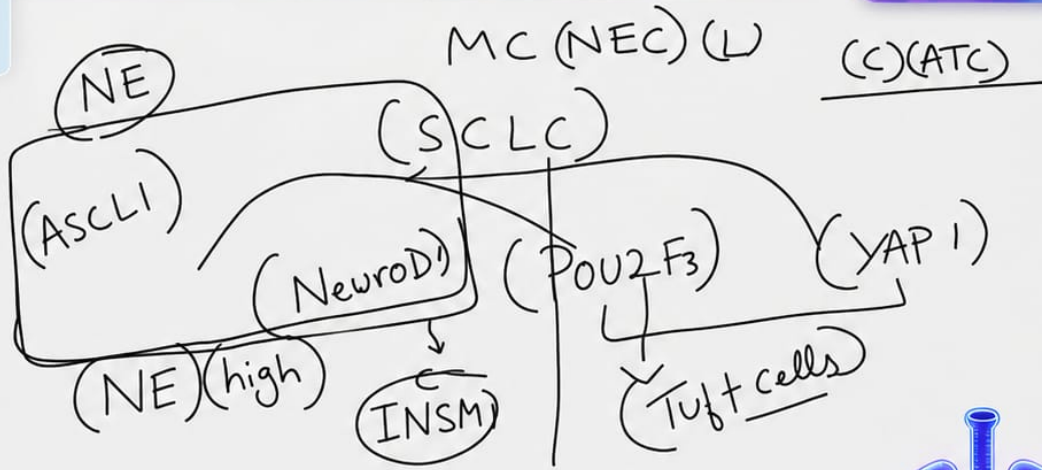


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Scroll AI content.  
Study from the  
**OG master.**



## MOLECULAR SUBTYPES OF SCLC



RECENT ADVANCES  
FOR MD EXAM



1

ASCL1  
(SCLC-A)



NE-HIGH

2

NEUROD1  
(SCLC-N)



NE-HIGH

3

POU2F3  
(SCLC-P)



NE-LOW / NEGATIVE

4

YAP1  
(SCLC-Y)



NE-LOW / NEGATIVE

### NEUROENDOCRINE-HIGH (NE-HIGH)



Synaptophysin



Chromogranin



CD56



**INSM1**  
BEST MARKER

### NEUROENDOCRINE-LOW / NEGATIVE (NE-LOW)



POU2F3 subtype  
associated with  
**TUFT CELLS**  
(chemosensory cells)



HIGH-YIELD CONCEPT  
FOR MD PATHOLOGY EXAM



MD/DNB  
Pathology



NEET-SS  
Pathology



FRCPath  
Part 1 & 2

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Master • Practice • Excel

Four transcription factors, four completely different personalities of small cell lung cancer. INSM1 is still the dependable one.

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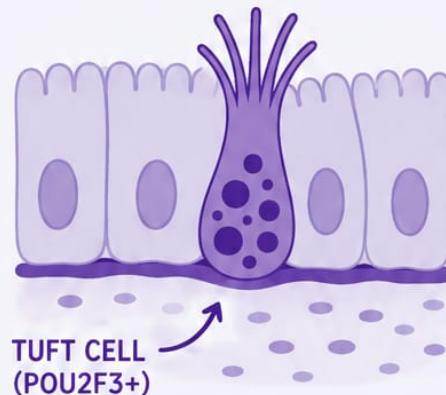
— PATH TO GLOBAL EXCELLENCE —

**WHAT YOU ARE  
NOT READING**  
**AND NOBODY IS  
TEACHING YOU**  
**SERIES**

# NOT ALL NEUROENDOCRINE TUMORS ARE POSITIVE FOR **CONVENTIONAL** **NEUROENDOCRINE** MARKERS!

Neuroendocrine tumors are a diverse group.

In **small cell tumors**, especially **lung**, and in **POU2F3-type NENs** arising from **tuft cells**, many can be **NEGATIVE** for conventional markers like **Synaptophysin** and **Chromogranin**.

**TAKEAWAY:**

If **Synaptophysin & Chromogranin** are negative in small cell tumors, especially lung, think **POU2F3** and do **IHC**!



Scroll AI content.  
Study from the **OG MASTER**.

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FRCPath™**— PATH TO GLOBAL EXCELLENCE —  
[www.elearningfrcpath.com](http://www.elearningfrcpath.com)

*Synaptophysin and chromogranin both go quiet, and it's still a neuroendocrine tumor. Blame the tuft cells.*

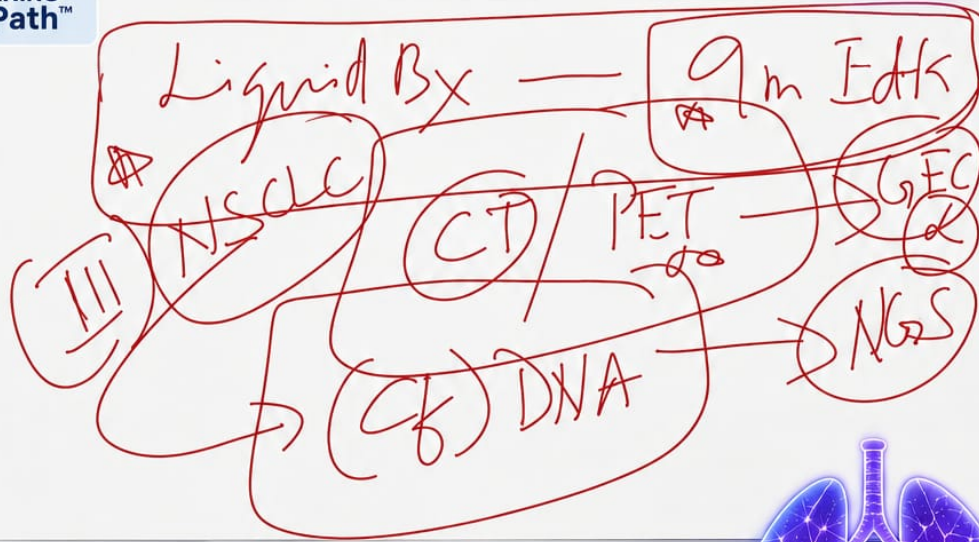


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Study from the  
**OG master.**



## LIQUID BIOPSY IN NSCLC



RECENT ADVANCE | MD PATHOLOGY EXAM

1



2M cases •  
1.8M deaths/year

2



Liquid biopsy →  
Stage III/IV  
NSCLC

3



9 mL EDTA  
blood sample

4



Tumor cfDNA  
in blood

5



NGS → EGFR &  
other actionable  
mutations



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Recent advances that every pathology resident should know.



Master the concepts.  
Ace your exams.  
Shape the future.



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Pathology



MD/DNB  
Pathology



DM  
Oncopathology

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9 mL of blood versus a needle biopsy. Ask the patient which one they'd rather have.

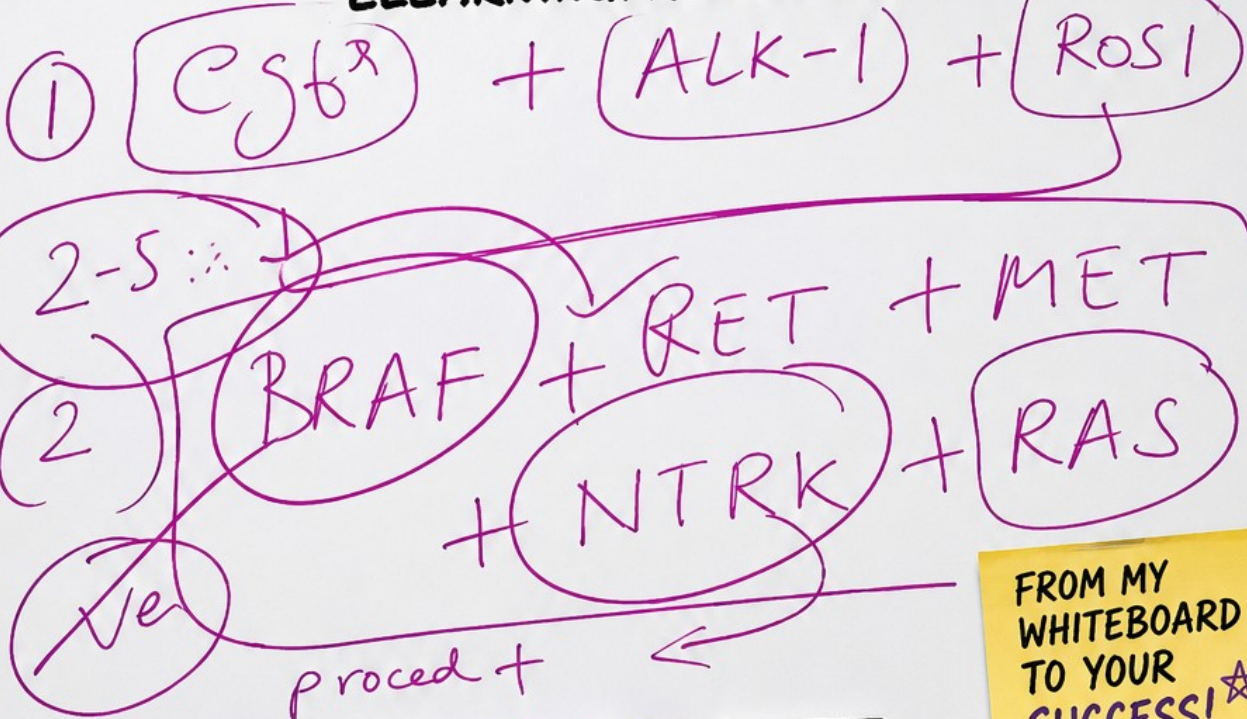
DON'T STOP  
AT NEGATIVE.  
GO DEEPER.  
FIND THE TARGET.

# LUNG ADENOCARCINOMA

## TIERED APPROACH TO MOLECULAR TESTING



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FROM MY  
WHITEBOARD  
TO YOUR  
SUCCESS! ☆

TIER  
**1**

### FIRST-LINE TESTING

Initial screening panel

EGFR

ALK-1

ROS1

IF NEGATIVE,  
DON'T STOP HERE!

TIER  
**2**

### SECOND-LINE TESTING

Broader panel – dig deeper

BRAF

RET

MET

NTRK

RAS



**2-5%**

These secondary alterations are rare – only **2% to 5%** of lung adenocarcinomas. But finding them is **GAME-CHANGING!**

**TARGETED THERAPIES THAT CHANGE OUTCOMES**

A negative first-line panel isn't the finish line. It's the "please continue" sign.

# 05

## CELL BIOLOGY & MECHANISMS OF DISEASE

---

*How cells actually die, scar, and switch their genes off.*

5 panels • maps to:

FRCPATH Part 1

MD/DNB Pathology

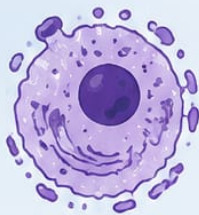
# THINGS HAVE MOVED BEYOND *APOPTOSIS*.

BUT ARE **YOU** UPDATED?

Modern pathology is decoding more.  
So should **you**.



## CELL DEATH: MORE THAN ONE WAY



### APOPTOSIS

Programmed  
Cell Death



### NECROPTOSIS

Regulated  
Necrosis



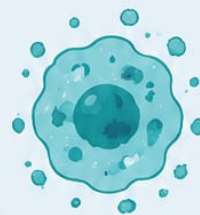
### PYROPTOSIS

Inflammatory  
Cell Death



### NETOSIS

Webs That  
Trap & Protect



### AUTOPHAGY

Cellular  
Self-Cleaning



## KEY PLAYERS YOU MUST KNOW



### CASPASE 3

Executioner  
of Apoptosis



### CASPASE 1

Master of  
Pyroptosis



### MLKL

Driver of  
Necroptosis



### MPO

Key Enzyme in  
NETosis

## STAY AHEAD. STAY UPDATED.

We cover what **really** matters — regularly.

AT **eLEARNINGFRCPATH™**



HIGH-YIELD  
CONCEPTS



UPDATED  
TOPICS



EXAM  
FOCUSED



MADE BY  
EXPERTS

Learn Smarter.  
Score Higher. 

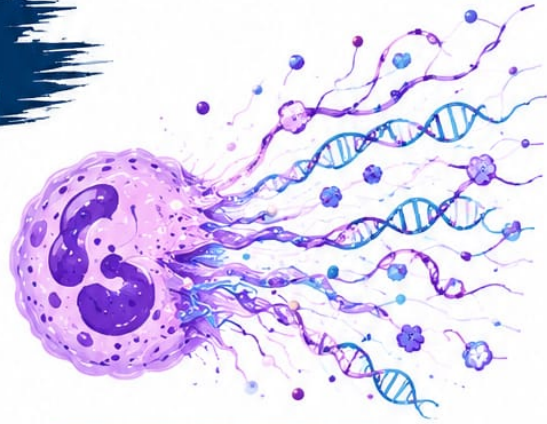
*Turns out cells have almost as many ways to die as pathology has ways to test you on it.*



WHAT YOU ARE NOT  
READING AND NOBODY  
IS TEACHING YOU **SERIES**

# NETOSIS

## THE DOUBLE EDGED SWORD OF **NEUTROPHILS**



NETosis is a specialized form of programmed **neutrophil cell death** (vital NETosis can occur without immediate cell death)

### NETS ARE MADE OF

- Decondensed chromatin (DNA & histones)
- Neutrophil Elastase (NE)
- Myeloperoxidase (MPO)
- Antimicrobial proteins

### WHAT NETS DO

- Trap and kill** microorganisms
- Cause collateral tissue injury** by histones, proteases and reactive oxygen species
- Activate endothelial cells** leading to endothelial dysfunction and microvascular damage
- Promote microthrombosis** and ischemic injury

### DISEASES WHERE NETOSIS MATTERS

- Sepsis
- Acute Respiratory Distress Syndrome (ARDS)
- COVID-19
- Vasculitis
- Ischemia-Reperfusion Injury

**NETOSIS**

PROTECTS  
AGAINST INFECTION



**BUT  
DAMAGES**

OUR OWN TISSUES

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YOUR HISTOPATHOLOGY COMPANION



SCROLL AI CONTENT.  
STUDY FROM THE **OG MASTER.**

*Neutrophils throwing their own DNA out like a net. Great against bacteria, rough on the neighbourhood.*

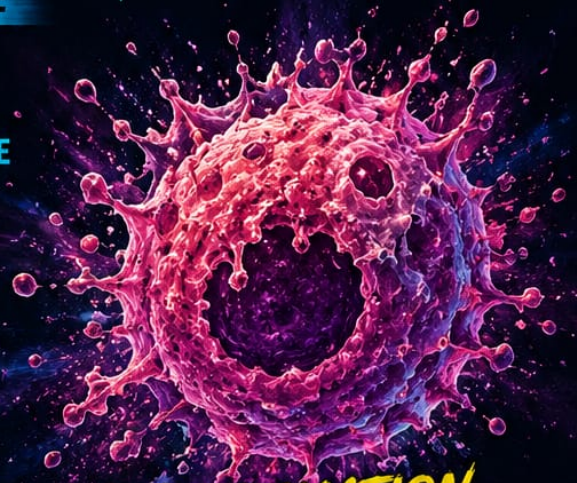
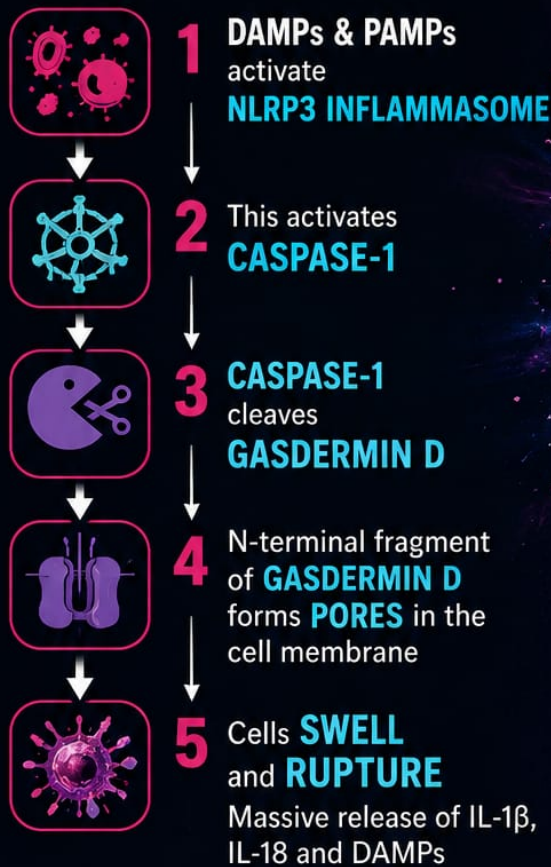
**WHAT YOU ARE NOT READING  
AND NOBODY IS TEACHING YOU**

# Pyroptosis IN ARDS

## THE PYROPTOSIS CASCADE



ARDS is now increasingly viewed as a disease driven by interconnected inflammatory cell-death pathways—particularly **PYROPTOSIS** and **NETOSIS**—rather than neutrophil-mediated injury alone.



**INFLAMMATION  
UNLEASHED!**

- Alveolar-capillary barrier **BREAKDOWN**
- Pulmonary **EDEMA**
- CYTOKINE STORM** AMPLIFICATION
- DIFFUSE ALVEOLAR DAMAGE**

### THE VICIOUS LOOP:

**Pyroptosis** → **NETosis** → More Inflammation  
A self-propagating cycle driving severe ARDS

### FUTURE THERAPIES:

Target **NLRP3** • **Caspase-1** • **Gasdermin D**  
**IL-1 Blockade** • **PAD4 Inhibition**

**SCROLL AI CONTENT. STUDY FROM THE OG MASTER.**

*One pore in the membrane, and suddenly the whole lung is having a very bad day.*

WHAT YOU ARE  
**NOT**  
READING



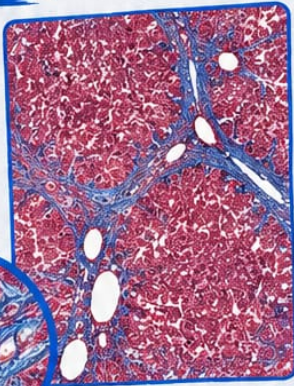
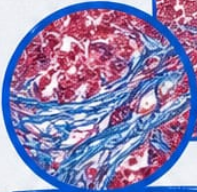
== SERIES ==

AND  
**NOBODY**  
IS TEACHING YOU

# FIBROSIS REMEMBERS. DO YOU?

**TRICHROME**

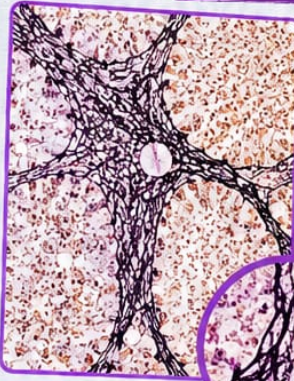
Tells you  
**HOW MUCH**  
**SCAR**  
the liver has.

COLLAGEN =  
QUANTITY

**ELASTIC STAINS**

Tells you  
**HOW LONG**  
the liver has  
**BEEN**  
**SCARRED.**




ELASTIN =  
TIME

 **TRICHROME** shows the **SCAR**.  
**ELASTIC STAINS** reveal the **STORY**. 

SESSION ON  
**MEDICAL**  
**LIVER DISEASE**  
FOR FRCPATH PART 1

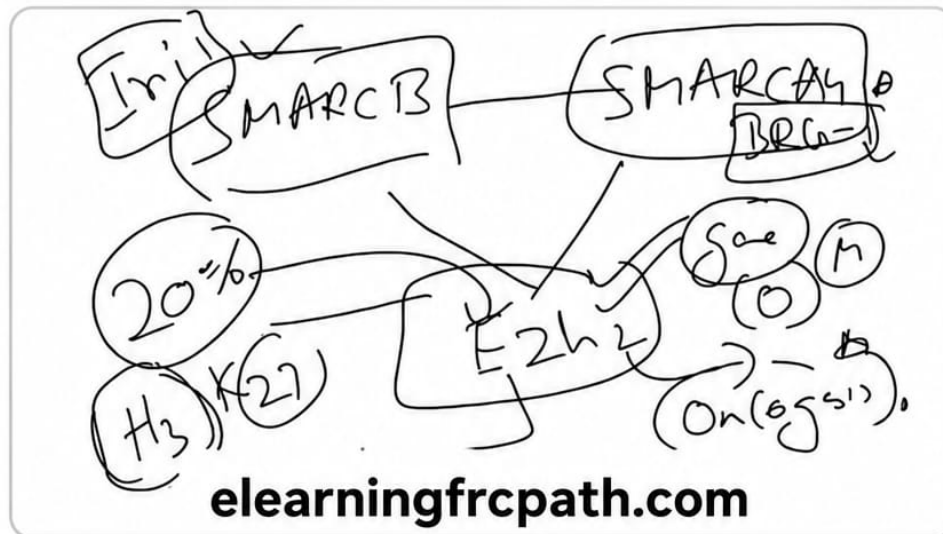
  
**TOMORROW**  
**8PM**  
INDIA TIME

BY  
**Dr Maitrayee Roy**  
FRCPATH

STAY AHEAD. STUDY SMART. **BE EXAM READY.**

ONLY ON  
**eLEARNINGFRCPATH™**

Trichrome counts how much damage happened. Elastic stain tells you how long ago it started. Together, basically the liver's diary.

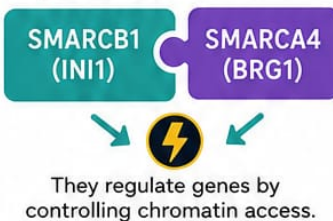


# THE EPIGENETIC BALANCE OF CANCER

When the balance breaks, cancer wins.

## 1 THE CORE INTERACTION

SMARCB1 and SMARCA4 work together as a chromatin-remodeling powerhouse.



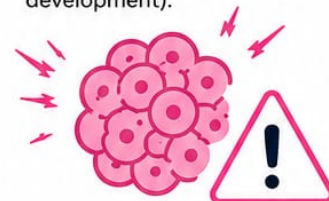
## 2 THE DOWNSTREAM TARGET

Working together, they control the expression of EZH2 (a histone methyltransferase).



## 3 THE ONCOGENIC MECHANISM

If EZH2 is mutated or overexpressed, it drives oncogenesis (tumor development).



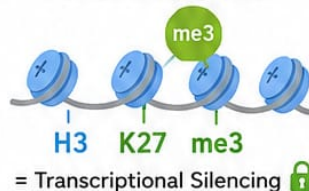
## 4 GENETIC ALIASES

Clinical / diagnostic names you'll see in reports.



## 5 THE EPIGENETIC MARK

EZH2 adds trimethyl groups to H3K27 → H3K27me3. This mark silences genes.



## 6 WHEN THE BALANCE BREAKS

If SMARCB1 or SMARCA4 is defective, EZH2 goes "UNCHECKED."  
→ Hyper-methylation  
→ Gene silencing  
→ Malignancy



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LEARN. REVISE. CRUSH IT.



SMARCB1 and SMARCA4 keep EZH2 in check. The second they clock out, EZH2 throws a party nobody invited.

# 06

## GYNECOLOGIC PATHOLOGY

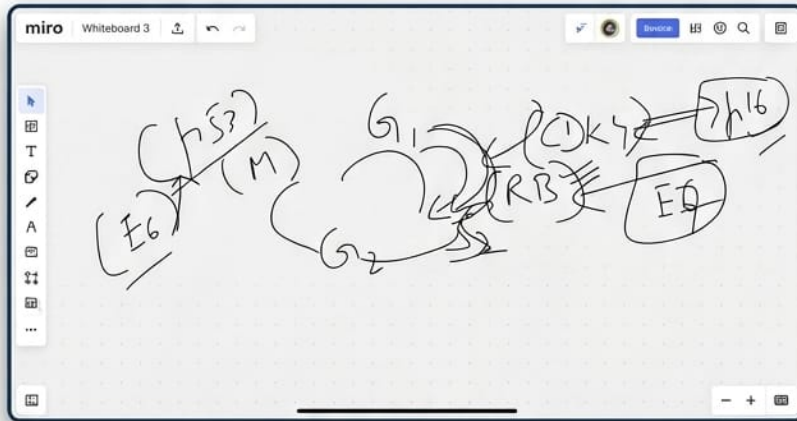
---

*Cervix, ovary and endometrium — where the exam loves to get specific.*

12 panels • maps to:

FRCPATH Part 1

# CUT THE COMPETITION: CRUSH THE HPV PATHWAY.



## 1. HPV'S DUAL THREAT



E7 DEGRADES RB  
E6 DESTROYS p53  
LIBERATING E2F

## 2. THE FEEDBACK LOOP



HYPERPROLIFERATION = STRESS!  
p16 SURGE TO SLOW DOWN

E2F STAYS UNBOUND! (p16 FAILS TO BIND)



## 3. CLINICAL EDGE



BLOCK p16 EXPRESSION IS KEY  
FOR DIAGNOSIS (HSIL/CxCa)



# MASTER THE FEEDBACK, OWN THE FRCPath EXAM.

E6 takes out p53, E7 takes out Rb. HPV really came in swinging with a two-for-one deal.

## Pop Quiz: Gynaec Cytology


**FRCPath Part 1**  
**MCQ**  
**TEST YOUR KNOWLEDGE!**

**SCROLL AI CONTENT.**  
**STUDY FROM THE**  
**OG MASTER.**

**Q.** A cervical screening sample is reported as **"?Invasive squamous cell carcinoma."**

What is the most appropriate next step?

- ☐ A Repeat cytology in 6 months
- ☐ B Repeat HPV testing
- ☐ C Routine colposcopy referral
- ☒ D Urgent suspected cancer (2-week wait) referral to gynaecological oncology
- ☐ E Excisional treatment without further assessment

**EXAM PEARL**

**"?INVASIVE SCC" CYTOLOGY REPORT = SUSPECTED CANCER**

**MANAGEMENT:** Urgent specialist assessment via **2-WEEK WAIT** pathway.




**GYNAEC CYTOLOGY**  
**LIVE MASTERCLASS**  
 — BY DR AKSHAY BALI —  
**TODAY** | **6:00 PM** (INDIA TIME) | FRCPath Part 1 Preparation


**SCROLL AI CONTENT.**  
**STUDY FROM THE OG MASTER.**

*"?Invasive SCC" on a cytology report is not a maybe. It's a two-week-wait referral wearing a disguise.*


**UPCOMING SESSION ON**  
**GYNAEC CYTOLOGY**  
**FRCPath Part 1**

**YOUR HISTOPATHOLOGY COMPANION**

**Q.** A 30-year-old woman participating in the NHS Cervical Screening Programme undergoes routine cervical screening. Her primary high-risk HPV test is negative.

According to the recent NHS screening update in England, when should she be invited for her next routine screening?

- ☐ A 12 months
- ☐ B 2 years
- ☐ C 3 years
- ☒ D 5 years
- ☐ E 10 years

**ANSWER** ✓

**5 YEARS**

From 1 July 2025, HPV-negative individuals aged 25–49 in England are recalled every 5 years.

**Why? A negative high-risk HPV test has a very high negative predictive value for CIN3+.**

**Smarter Screening. Better Prevention.**

**STUDY SMART. SCREEN BETTER.**  
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500+ HOURS RECORDED CONTENT | HIGH-YIELD NOTES | MCQ & MOCK TESTS | LIFETIME VALIDITY

JOIN US & ACE FRCPath Part 1

*A negative HPV test just bought her five years off, not five months of worry.*

*Two cards, zero excuses for missing this on the exam.*

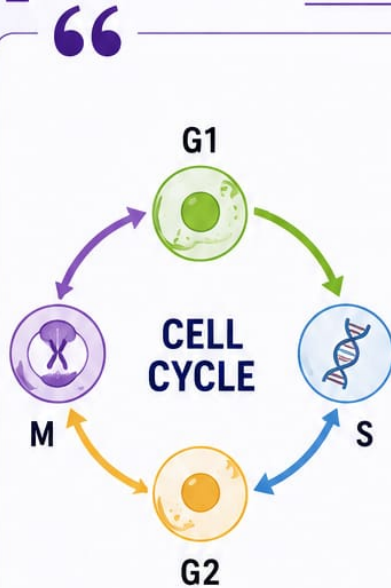


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WHAT YOU ARE  
NOT READING  
AND NOBODY  
IS TEACHING YOU  
**SERIES**

# p16 OVEREXPRESSION



Diffuse **p16** positivity  
is a marker of

**CELL-CYCLE DEREGULATION,**

not proof of  
HPV infection or  
cervical origin.

Always interpret p16 in conjunction  
with morphology and a broader  
immunohistochemical panel.

## p16 OVEREXPRESSION CAN BE SEEN IN:



Cervical  
SCC/HSIL



HPV-associated  
Oropharyngeal  
SCC



Anal, Vulvar,  
Vaginal, Penile  
SCC



Urothelial  
Carcinoma



High-grade Serous  
Ovarian Carcinoma



Endometrial  
Serous Carcinoma



p16 positivity reflects Rb pathway inactivation, not necessarily HPV infection or cervical origin.



**KNOW**  
BEYOND  
THE TEXTBOOK



**THINK**  
LIKE AN  
EXAMINER



**FOCUS ON**  
WHAT REALLY  
MATTERS



**LEARN.**  
REVISE.  
RECALL.  
REPEAT.



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Follow us



*p16 positive means the cell cycle broke. It doesn't, by itself, tell you who broke it. Read the room.*

WHAT YOU'RE NOT READING  
& NOBODY IS TEACHING YOU SERIES

eLEARNING  
FRCPATH™  
SMARTER LEARNING. STRONGER YOU.

HGSOC: THE SILENT SPREADER

# ANOIKIS RESISTANCE

THE GAME CHANGER IN OVARIAN CANCER

Not just cells. It's strategy.  
Not in blood. Not by luck. **By design.**



- 1 DETACH**  
  
Cells shed from fallopian tube fimbriae into peritoneal fluid. Detachment stress is real.
- 2 CLUMP**  
  
They form 3D spheroids to avoid anoikis & stay alive.
- 3 HIDE & SURVIVE**  
  
Recruit normal cells (like fibroblasts) to build a survival shield. Fake matrix. **Real protection.**

**LIVE** ((•))

## OVARIAN TUMORS

**LIVE SESSION**

**COMING SOON**  
STAY TUNED. LEVEL UP.



**REAL SCIENCE. SIMPLIFIED.**

**BEYOND TEXTBOOKS.**

**BUILT FOR GEN Z MINDS.**

**SMARTER TODAY.  
STRONGER TOMORROW.**

SAVE THE DATE | SHARE WITH YOUR SQUAD | DON'T MISS IT

Detach, clump up, recruit a few fibroblasts as bodyguards. Ovarian cancer cells have an actual survival strategy, and it's a good one.



# DID YOU KNOW?

## BRCA NEGATIVE CAN STILL BE HRD POSITIVE!



**BRCA1/2** negative in blood and tumor,  
but **HRD positive** due to other HR gene  
alterations.

### 1. BLOOD TEST



**BRCA1/2  
NEGATIVE**



### 2. TUMOR TEST



**BRCA1/2  
NEGATIVE**



### 3. HRD TEST



**HRD  
POSITIVE**

### WHY CAN THIS HAPPEN?

Alterations in other HR genes can  
cause HRD.

RAD51C

RAD51D

PALB2

ATM

ATR

BRIP1

CHEK2

FANCA

FANCD2

FANCL

NBN



### HRD SCORE (GENOMIC SCARS)

**HRD Score = LOH + TAI + LST**

**LOH**

Loss of  
Heterozygosity

**18**

**TAI**

Telomeric  
Allelic Imbalance

**15**

**LST**

Large-Scale  
State Transitions

**12**

**HRD SCORE = 18 + 15 + 12 = 45**  
(≥42 = HRD Positive\*)



### TAKEAWAY

HRD-positive tumors may still benefit from **PARP inhibitor therapy**,  
even if BRCA is negative.

★ LEARN • REVISE • EXCEL

eLEARNING FRCPATH™

*Clean BRCA result, broken repair pathway anyway. The tumor found a workaround.*

**eLEARNING  
FRCPATH™****TM**

# EXPANSILE INVASION IN OVARIAN MUCINOUS TUMORS

**WHO CRITERIA YOU MUST KNOW****DEFINED AS:**

Confluent glandular/  
cribriform growth



With minimal  
intervening stroma



Measuring  $\geq 5$  mm  
in greatest linear dimension

**OR**

Occupying an area  
 $\geq 10$  mm<sup>2</sup>

**SIZE MATTERS.  
STROMA MATTERS.**



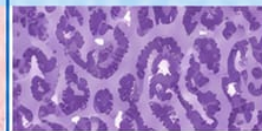
Once this threshold is exceeded,  
the lesion is classified as

**EXPANSILE INVASIVE  
MUCINOUS CARCINOMA**

rather than borderline tumor.

**BORDERLINE TUMOR**

Glands separated  
by stroma

**EXPANSILE INVASIVE  
CARCINOMA**

Confluent glands with  
minimal/no stroma



**UPCOMING SESSION  
OVARIAN TUMORS**

High yield. Exam focused. Pathology made simple.



**STAY AHEAD.  
PATH SMART.**

with eLEARNINGFRCPATH™

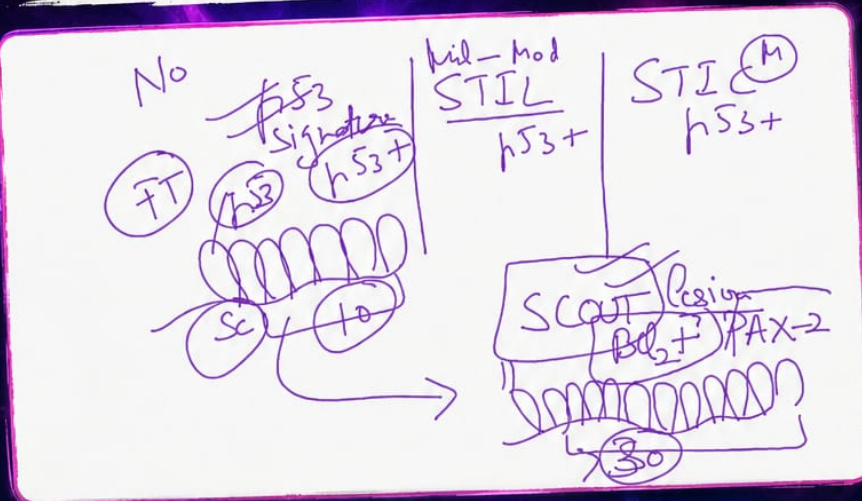
*5mm is all it takes to flip "borderline" into "call the oncologist."*

# WHAT YOU ARE **NOT** READING AND **NOBODY** IS TEACHING YOU



THE  
WHITEBOARD  
YOU WISH  
YOU HAD  
IN CLASS!

★  
High-yield  
Concepts.  
Simplified.  
Remembered  
Forever.



## SCOUT LESIONS

### SECRETORY CELL OUTGROWTH



**SCOUT** lesions refer to **secretory cell outgrowth**.

The fallopian tube has **2** cell types:

**Ciliated Cells** & **Secretory Cells**.



To identify a SCOUT lesion, you must find:

- ✓ **30+** consecutive secretory cells
- ✓ **NO** ciliated cells at all.



These cells show:

- ✓ Overexpression of **BCL2**
- ✓ Loss of **PAX2** expression



**HIGHLY SIGNIFICANT**

**75%** of ovarian tumors are  
High-Grade Serous Ovarian Carcinomas.



CAN'T AVOID THEM.  
MUST UNDERSTAND THEM.  
KNOW THE **PATH**.  
BEAT THE **DISEASE**.

UPCOMING  
SESSION

## OVARIAN TUMORS

Pathogenesis | Precursor Lesions | High-Yield Pearls

LEARN **SMART**. THINK **PATH**. STAY **AHEAD**.

@eLearningFRCpath



DON'T JUST  
STUDY.  
UNDERSTAND.  
REMEMBER.  
CRUSH IT.

Thirty secretory cells in a row, zero ciliated cells in sight. The fallopian tube's way of raising an early red flag.



# TWO CANCERS. TWO GATEKEEPERS. **TWO LEGENDS.**

## APC

THE FAMOUS ONE  
THE GATEKEEPER OF  
COLON CANCER



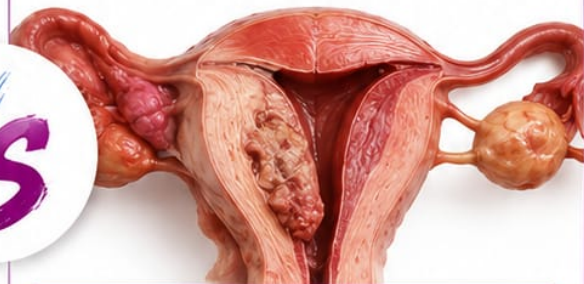
APC loss is the  
earliest step in  
colorectal cancer.



Classic. Taught.  
Well known.

## PTEN

THE LESSER KNOWN VILLAIN  
THE GATEKEEPER OF  
ENDOMETRIAL CANCER



PTEN loss is the  
most common  
and earliest mutation  
in endometrial carcinoma.



Real. Powerful.  
Underappreciated.

VS

**IF APC = COLON CANCER,  
THEN PTEN = ENDOMETRIAL CANCER.** 



KNOW  
THE PATH.



RESPECT THE  
GATEKEEPERS.



CRACK  
THE EXAM.

eLEARNINGFRCPATH™ – LEARNING THAT HITS DIFFERENT.

APC gets all the textbook fame for colon cancer. PTEN has quietly been running the same show in the endometrium the whole time.



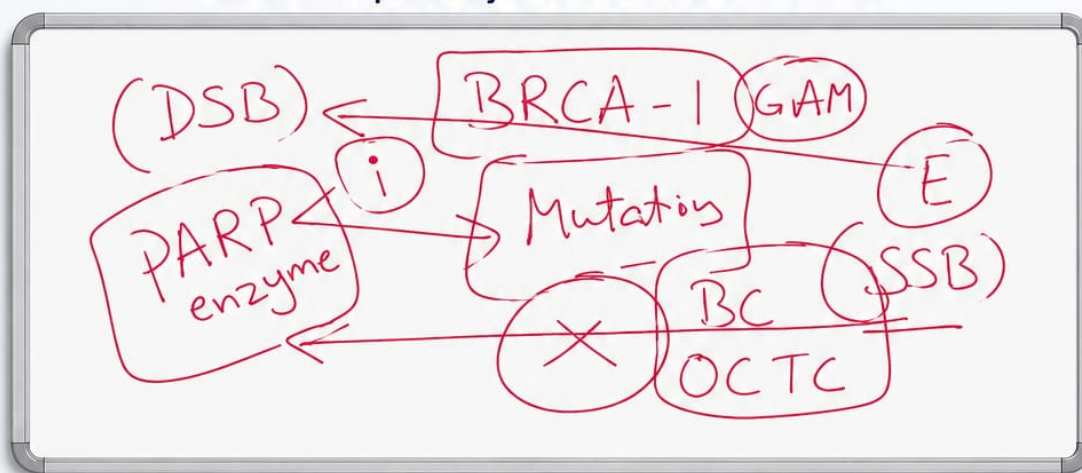
# eLEARNING FRCPATH™

Your Path to Excellence

FRCPath | NEET-SS Pathology

## CRACK THE CODE. KILL THE CANCER.

Master the pathway. Ace the exam. **Save lives.**



### THE BIG IDEA (IN SIMPLE STEPS)

#### 1 THE PROBLEM

BRCA-1 mutation breaks the body's main DNA repair system (HR).



Double-stranded breaks (DSBs) can't be fixed. Mutations build up.

#### 2 THE BACKUP

Cells survive using a backup system: PARP enzyme repairs single-strand breaks (SSBs).



The cancer cell becomes **ADDICTED** to PARP for survival.

#### 3 THE STRATEGY

Block PARP, the backup fails. SSBs accumulate and collapse into deadly DSBs.



No escape. The cancer cell **has to die.**

#### 4 THE WONDER DRUG

PARP inhibitors (e.g., Olaparib) shut down the backup and target cancer cells with BRCA-1 mutations.



Targeted therapy. Better outcomes. More hope.



### KNOW THE PATHWAY. CHANGE OUTCOMES.

Concept clarity today. Clinical impact tomorrow.



High-Yield Concepts



Exam Focused



Clever Visuals Better Retention



Top Rankers Trust Us

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Your exam journey begins here.

Take away the backup DNA repair system, and the cancer cell genuinely has nowhere left to go. That's the entire strategy.



# THE BIG TRAP

## NOT ALL ENDOMETRIAL TUMORS ARE ER/PR POSITIVE!

**CONVENTIONAL THINKING IS WRONG.**

Not all endometrial carcinomas arise from the estrogen pathway.

### HIGH-GRADE ENDOMETRIAL CARCINOMAS

**USUALLY ER/PR NEGATIVE**

#### CLEAR CELL CARCINOMA



**ER - PR -**

Napsin A +  
HNF1β +

#### SEROUS CARCINOMA



**ER - PR -**

p53 abnormal  
p16 diffuse +

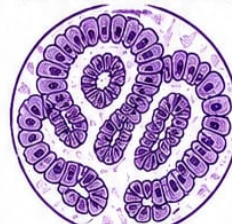
#### MESONEPHRIC-LIKE ADENOCARCINOMA



**ER - PR -**

TTF-1 +  
GATA3 +

#### ENDOMETRIOID CARCINOMA (ESTROGEN-DRIVEN)



**ER + PR +**

Often PTEN, PIK3CA,  
MMR, POLE



**DON'T ASSUME ER/PR POSITIVITY.**

**ALWAYS USE A PANEL. THINK MORPHOLOGY + IHC + MOLECULAR.**

#### QUICK CHECK



Uterine carcinoma  
ER/PR negative?



Check  
PAX8



Use panel:  
TTF-1, GATA3,  
Napsin A, HNF1β,  
p53, p16



Arrive at the  
correct diagnosis

**eLEARNING FRCPATH™**

LEARN SMART. DIAGNOSE BETTER. EXCEL ALWAYS.



Assuming every endometrial cancer is hormone-driven is exactly how marks get lost on this question.



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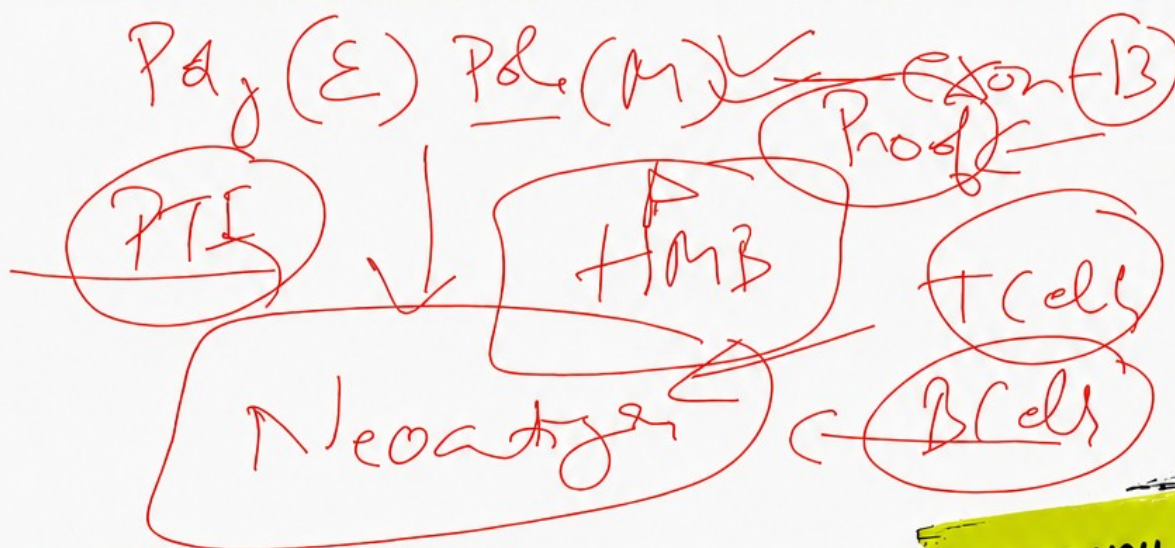
Learn Smart.



Score High.



Stay Ahead.



# POLE MUTATION: THE IMMUNE MAGNET

WHAT YOU ARE  
NOT READING.  
AND NOBODY IS  
TEACHING YOU.

## 1. THE SPARK

POLE mutation  
(most common in  
exon-13)



POLE is a proofreading  
enzyme. Mutation =  
loss of function.  
DNA repair? Compromised.

**FIRST STEP TO  
THE CASCADE!**

## 2. THE CASCADE

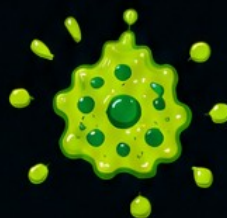
No proofreading  
= more mistakes  
= High Mutation  
Burden (HMB)



**MORE MUTATIONS.  
MORE CHAOS.**

## 3. THE SIGNAL

High mutation burden  
creates **NEOANTIGENS**



Neoantigens act like  
a signal flare!

**THE BODY GETS  
THE MESSAGE.**

## 4. THE RESPONSE

Neoantigens attract  
the immune squad:



Result? High  
Peritumoral Infiltration  
(PTI)

**IMMUNE CELLS  
SHOW UP IN FORCE!**

A proofreading enzyme breaks, mutations pile up, and somehow that mess is why the immune system shows up in force. Cancer biology, everyone.

# 07

## GENITOURINARY PATHOLOGY: PROSTATE & BLADDER

---

*Gleason grades, PTEN, and the variants that change management.*

7 panels • maps to:

NEET-SS Pathology

FRCPATH Part 1

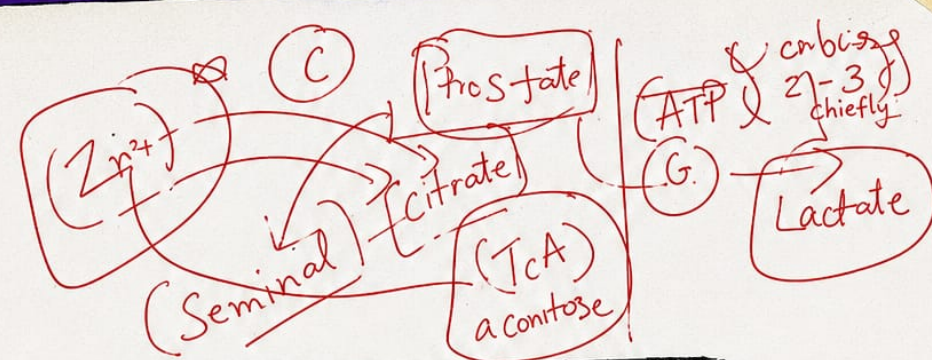


# WHAT ARE **NOT** READING & NOBODY IS TEACHING YOU...



Understand Pathogenesis

UNLOCK THE **SECRET** METABOLIC FLIP IN PROSTATE CANCER!



**THE OPPOSITE WARBURG EFFECT**

### NORMAL PROSTATE

-  Zinc ( $Zn^{2+}$ ) is actively pumped in
- ↓
-  Zinc inhibits Aconitase
- ↓
-  TCA cycle is halted  
Citrate accumulates
- ↓
-  Citrate secreted into seminal fluid
- ↓
-  Low ATP production  
(2-3 ATP via glycolysis)  
Glycolysis chiefly

Energy Low! 😞

VS

### PROSTATE CANCER

-  Zinc pump is **lost**
- ↓
-  Aconitase is **no longer** inhibited
- ↓
-  TCA cycle is **UNLEASHED**
- ↓
-   $\beta$ -Oxidation of fatty acids  
→ Acetyl-CoA ↑↑
- ↓
-  High ATP production  
(20-30 ATP via TCA)  
Energy machine **ON!**

TCA Full Speed! ⚡

Massive Energy! ⚡

**PROSTATE CANCER RUNS ON TCA, NOT GLYCOLYSIS!**



**Normal prostate:**  
Makes **citrate**.  
Not energy.



**Prostate cancer:**  
Makes **energy**.  
Not citrate.

**THIS FLIP FUELS PROGRESSION!**





eLearningFRCPath.com



Concepts that Stick



Pathogenesis made Easy



High Yield for Exams

**STUDY SMART.  
STAY AHEAD.  
BE THE EXCEPTION.**

Normal prostate cells make citrate and call it a day. Cancer cells flip the switch and start making energy instead. Overachievers.



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High Yield. Exam Focused. Results Driven.

**CLASS  
TODAY!**



# PATHOLOGY POWER HOUR

PROSTATE & URINARY BLADDER



HIGH YIELD



EXAM FOCUSED



RESULTS DRIVEN

## KEY GRADING DIFFERENCES

| FEATURE                                                                                                     | TURP / ENUCLEATION SPECIMEN                                          | RADICAL PROSTATECTOMY (RP) SPECIMEN                                                                    |
|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
|  Primary Pattern         | Most common pattern.                                                 | Most common pattern.                                                                                   |
|  Secondary Pattern       | Highest grade pattern present (even if it accounts for < 5%).        | Second most common pattern.                                                                            |
|  Minor High-Grade (< 5%) | Directly included in the main Gleason Score as the secondary number. | Reported separately as a <b>Tertiary Pattern</b> ; does not change the core Gleason Score/Grade Group. |
|  Minor Low-Grade (< 5%)  | Ignored.                                                             | Ignored.                                                                                               |



**TODAY**  
**6:00 PM**  
— INDIA TIME —

*BE THERE. LEARN BETTER.  
SCORE HIGHER.*



**JOIN LIVE. STAY AHEAD.**



[www.elearningfrcpath.com](http://www.elearningfrcpath.com)

Same 5% tumor, two completely different rules depending on which specimen it landed in. The exam loves this exact detail.

# DID YOU KNOW?

## GSTP1

(GLUTATHIONE S-TRANSFERASE **PI 1**)

### THE EARLIEST EVENT IN PROSTATE CANCER

**GSTP1 ACTIVE**



Detoxifies harmful agents and **protects** your **DNA**

**GSTP1 HYPERMETHYLATION**  
(SILENCES THE GENE)



Promoter **hypermethylation** switches off GSTP1 gene

**DEFENSE LOST**



Oxidative **damage** builds up

**LEADS TO PROSTATE CANCER**

**UNDERSTAND PATHOGENESIS.**

Cancer doesn't start with a mutation. It starts when the cell's **antioxidant shield** was switched off.



SESSION ON  
**PROSTATE &  
URINARY BLADDER  
PATHOLOGY**



**SATURDAY  
6:00 PM  
(INDIA TIME)**



**Dr. Akshay Bali**  
NEET SS PATHOLOGY  
FRCPath PART 1



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FRCPath™**  
BOLD. FOCUSED. PATHOLOGY.



SCROLL AI CONTENT.



STUDY FROM THE OG MASTER.

Cancer doesn't always start with a bang. Sometimes it starts with the antioxidant shield quietly getting switched off.

# IDC-P vs CRIBRIFORM ADENOCARCINOMA

**SAME CRIBRIFORM. DIFFERENT CRIME SCENE.**



## IDC-P (INTRADUCTAL CARCINOMA OF PROSTATE)

### LUXURY APARTMENT Inside the pre-existing duct

We're dangerous... but we're still inside the building.

Nobody crossed the basement membrane.

SECURITY

SECURITY

Don't look at the holes. Look at the border.

- ✓ Basal cells present (at least focally)
- ✓ Intraductal location (within ducts/acini)
- ✓ Marked nuclear pleomorphism common
- ✓ Comedonecrosis common

## CRIBRIFORM ADENOCARCINOMA (INVASIVE)

### PRISON BREAK Invades the stroma

We escaped. The stroma belongs to us now!

NO BASAL CELLS BEYOND THIS POINT

- ✗ Basal cells absent
- ➔ Stromal invasion present
- ➔ Gleason Pattern 4 (Cribriform = Pattern 4)



Dead cell trap in the center (Comedonecrosis) can occur in BOTH.

**NOT A RELIABLE DIFFERENTIATOR!**



Basal cells win every time. ★

## QUICK GUIDE



**BASAL CELLS PRESENT?**

Think **IDC-P**  
(Intraductal)

**VS**



**BASAL CELLS ABSENT?**

Think **Cribriform Adenocarcinoma**  
(Invasive, Gleason Pattern 4)



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Scroll AI content.  
Study from the OG master.

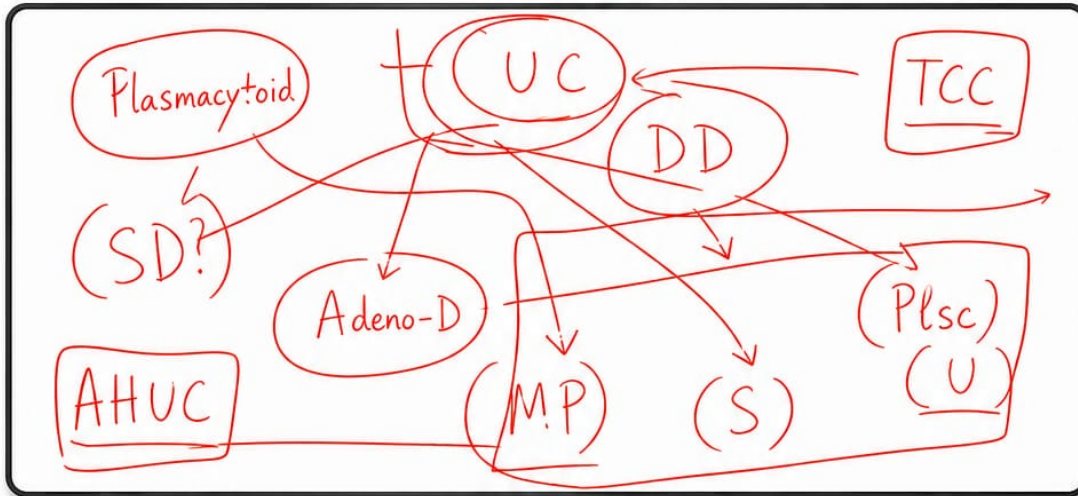
Same cribriform pattern, same ugly nuclei. Only one of them actually broke out of the duct — the basal cells are the bouncers who decide which.



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FRCPATH™**  
MASTER PATHOLOGY. OWN YOUR FUTURE.

# UROTHELIAL CARCINOMA

**NOT ALL VARIANTS ARE  
CREATED EQUAL**



**KNOW THESE 3. THEY CHANGE MANAGEMENT.**

**1**

**MICROPAPILLARY  
VARIANT (MP)**



Aggressive behavior  
& early metastasis.

**HIGH-RISK VARIANT**

**2**

**SARCOMATOID  
VARIANT (S)**



Biphasic malignant epithelial  
& mesenchymal components.

**HIGH-RISK VARIANT**

**3**

**PLASMACYTOID  
VARIANT (P/Plsc)**



Discohesive cells.  
Deep infiltration & high rate  
of peritoneal recurrence.

**HIGH-RISK VARIANT**

## SD & GLANDULAR DIFFERENTIATION

✓ Squamous differentiation (SD)  
within high-grade UC → Usually does **NOT**  
worsen prognosis

✓ Adenocarcinoma / glandular  
differentiation (AD/AdicD) → Usually does **NOT**  
worsen prognosis



Studies contradictory,  
but general management doesn't  
change for these findings alone.



## EXAM PEARL

- ! Micropapillary
- ! Sarcomatoid
- ! Plasmacytoid

**= MANAGEMENT-  
CHANGING  
VARIANTS**

**SD & GLANDULAR?** 🤔

→ **USUALLY NOT A BIG DEAL.**

**MP, SARCOMATOID &  
PLASMACYTOID?** 🦴

→ **PAY ATTENTION.**



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Pathology



Exam-focused  
Learning



Built for  
Future Docs

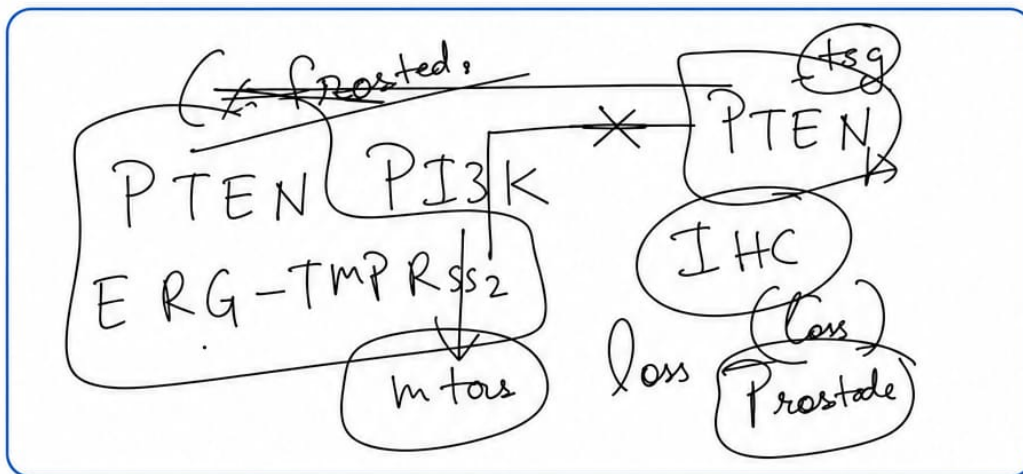
**LEARN DIFFERENT.  
SCORE HIGHER.  
STAY AHEAD.**

*Micropapillary, sarcomatoid, plasmacytoid. Three words that quietly rewrite the whole management plan.*



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## DID YOU KNOW?

**PTEN IS THE BRAKE. WHEN IT'S LOST, PROSTATE CANCER HITS THE GAS.**

### THE PTEN/PI3K/mTOR PATHWAY



**PTEN**

Tumor suppressor  
(THE BRAKE)  
Loss/Mutation **X**



**PI3K**

Gets activated  
when PTEN  
is lost



**mTOR**

Drives growth,  
survival &  
proliferation



**OUTCOME**

Promotes prostate  
cancer progression  
& resistance

### DIAGNOSTIC RELEVANCE



#### PTEN LOSS

by IHC is a key  
diagnostic marker  
in prostate cancer.



Often seen in  
**ERG-TMPRSS2**  
fusion-positive  
tumors.



Helps in risk  
stratification &  
prognosis.



**UNDERSTAND THE PATHWAY.  
DIAGNOSE WITH IMPACT.  
DELIVER BETTER OUTCOMES.**



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Future Docs

**LEARN DIFFERENT.  
SCORE HIGHER.  
STAY AHEAD.**

*PTEN is the brake pedal. Lose it, and prostate cancer finds the accelerator.*



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FRCPath™**  
Your Histopathology Companion

# TERT THE IMMORTALITY SWITCH



TERT promoter mutations **reactivate telomerase**, **stabilize telomeres**, and confer **cellular immortality**—one of the defining hallmarks of malignant transformation.



## THYROID FNAs

**GREATEST CLINICAL UTILITY**



**Indeterminate FNAs**  
(Bethesda III, IV,  
and selected V)



TERT mutation alone  
strongly suggests  
**MALIGNANCY.**



Improves risk stratification



Helps guide extent  
of surgery



## URINE CYTOLOGY

**EARLY. SENSITIVE. SMART.**

TERT promoter mutations occur  
**very early** in urothelial carcinoma.

### ADVANTAGES



Detects **low-grade tumors**  
that may be missed by  
urine cytology.



**Higher sensitivity**  
than cytology alone.



Useful in **surveillance**  
for recurrent bladder cancer.



Can detect recurrence  
**early**—before it is visible.



**TERT ISN'T JUST A MARKER.  
IT'S A GAME CHANGER.**



Scroll AI content.  
Study from the **OG master**.



Trusted by Thousands  
of Pathologists  
Across India & Globally



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FRCPath

NEET-SS

DM Oncopathology



One mutation in a promoter region and the cell simply forgets how to grow old. Thyroid and bladder both fall for it.

# 08

## RENAL PATHOLOGY: MEDICAL & NEOPLASTIC

---

*From glomeruli to pediatric renal tumors — the biggest chapter in the book, for a reason.*

15 panels • maps to:

NEET-SS Pathology

FRCPATH Part 2

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LEARN • UNDERSTAND • EXCEL

Case of

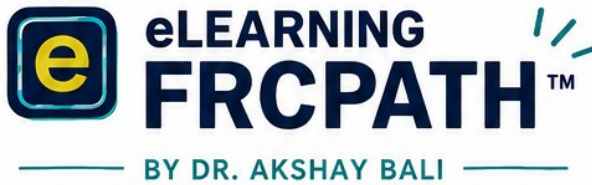
# HYDATID CYST

## INVOLVING KIDNEY

Multiple hydatid cysts replacing renal parenchyma with daughter cysts and hydatid sand.

**HIGH YIELD  
PATHOLOGY****REAL CASES  
REAL LEARNING****VISUALS THAT  
MAKE SENSE****LEARN PATHOLOGY THE GEN Z WAY! ⚡**[elearningfrcpath.com](https://elearningfrcpath.com)[@elearningfrcpath](https://www.instagram.com/elearningfrcpath)

*Daughter cysts, hydatid sand, and a gross specimen photo that never fails to make the whole room go quiet.*



SCROLL AI CONTENT.  
STUDY FROM THE OG MASTER 🧐

# ANTI-PLA2R

THE REAL **VILLAIN** IN  
MEMBRANOUS NEPHROPATHY

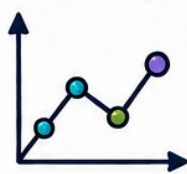


PLA2R =  
THE REAL  
**DEAL**



~100%  
**SPECIFIC**

Not seen in other  
kidney diseases  
or healthy  
controls.



**TITER  
MATTERS**

↓ Disappears →  
Remission  
↑ Reappears →  
Relapse



**LOW / MOD  
TITERS**

More chance of  
spontaneous  
remission



**HIGH  
TITERS**

Progression of  
proteinuria &  
decline in  
kidney function



**WHERE IS  
PLA2R1?**

Podocytes  
+ neutrophils,  
lung macrophages,  
airway & submucosal  
epithelial cells



**REMEMBER!**

Monitor titer.  
Guide therapy.  
Improve outcomes. ❤️



UPCOMING SESSION

**MEDICAL KIDNEY DISEASE**

FOR NEET SS PATHOLOGY / FRCPATH PART 1



TOMORROW



6:00 PM  
(INDIA TIME)

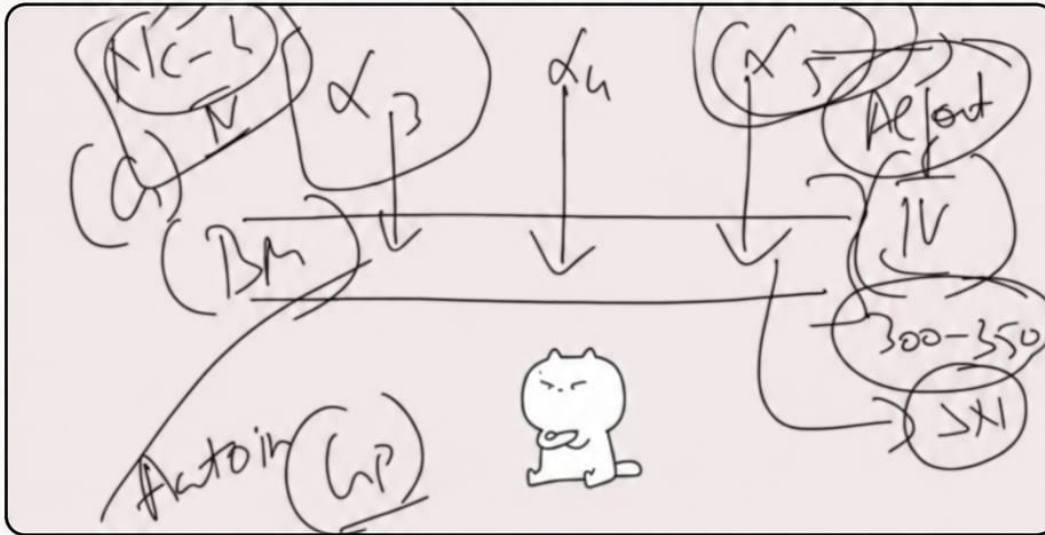


BY  
DR. AKSHAY BALI

**DON'T  
MISS IT!**

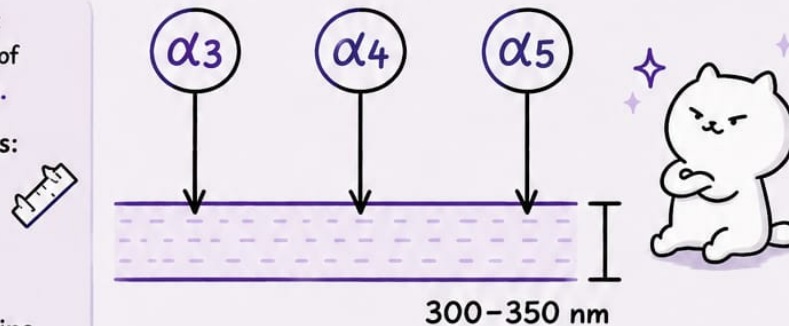
Titer drops, patient goes into remission. Titer creeps back up, so does the proteinuria. PLA2R does not do subtly.

# ≡ ELEARNINGFRCPATH.COM ≡



## 1. STRUCTURE & NORMAL CHARACTERISTICS

- ☆ **Key Component:**  
GBM is composed of Type IV collagen.
- ☆ **Normal Thickness:**  
300 – 350 nm
- ☆ **Alpha Chains:**  
Type IV collagen consists of  $\alpha 3$ ,  $\alpha 4$ ,  $\alpha 5$  chains.



## 2. ASSOCIATED CLINICAL SYNDROMES

### GOODPASTURE SYNDROME



**Classification:**  
Autoimmune disorder.



**Mechanism:**  
Autoantibodies target the  $\alpha 3$  chain (NC1) of Type IV collagen (anti-NC3 Type IV collagen antibodies).



**Pathology:**  
Autoantibodies deposit along the basement membrane.

### ALPORT SYNDROME



**Classification:**  
Genetic disorder (X-linked).



**Mechanism:**  
Defective gene that fails to properly code for the  $\alpha 5$  chain of Type IV collagen.

#### Clinical Triad:



**Glomerular Dysfunction**  
(hematuria, proteinuria)



**Sensorineural Deafness**  
(progressive hearing loss)



**Eye Defects**  
(lenticonus, retinopathy)



**KNOW THE MEMBRANE.  
DIAGNOSE WITH CONFIDENCE.**

ELEARNINGFRCPATH.COM

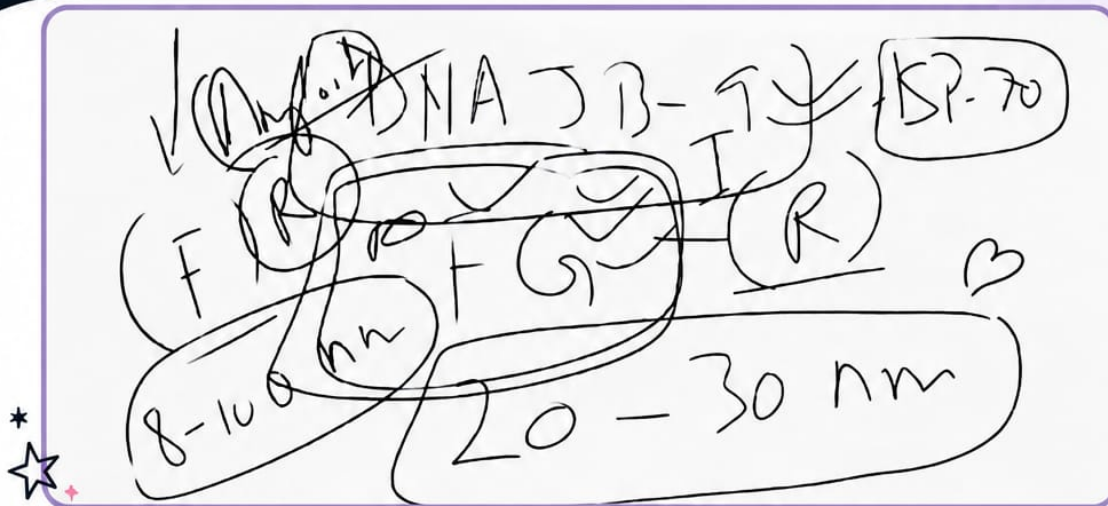


Same collagen chain — attacked by antibodies in one disease, never built properly in the other. The kidney loses either way.



**eLEARNING**  
**FRCPath**

LEARN  
**SMARTER,**  
NOT HARDER



# FGN VS. AMYLOIDOSIS

KNOW THE DIFFERENCE. **DIAGNOSE WITH CONFIDENCE.**



## KEY DIAGNOSTIC MARKER

- ✓ **DNAJB9** has been identified as a highly specific diagnostic biomarker for fibrillary glomerulonephritis (FGN).
- ✓ It is a member of the Heat Shock Protein 70 (**HSP-70**) co-chaperone family.
- ✓ DNAJB9 serves as an immunohistochemistry (**IHC**) marker to accurately differentiate FGN from other mimicking renal diseases.



## ULTRASTRUCTURAL DIFFERENCES (FIBRIL SIZE)

While both diseases feature extracellular, randomly arranged fibril deposits, they differ significantly under electron microscopy:

|                                                                                                     | FIBRILLARY<br>GLOMERULONEPHRITIS (FGN) | VS. | AMYLOIDOSIS       |
|-----------------------------------------------------------------------------------------------------|----------------------------------------|-----|-------------------|
|  FIBRIL DIAMETER | 20 – 30 nm                             |     | 8 – 10 nm         |
|  ARRANGEMENT     | Randomly arranged                      |     | Randomly arranged |
|  PREVALENCE      | Very rare renal disease                |     | More common       |



**PATHOLOGY IS COOL.**  
**YOU'VE GOT THIS!**



**eLEARNING**  
**FRCPath**

**FOLLOW & LEARN!**



Both look like a tangle of random fibrils on EM. Only the ruler — and DNAJB9 — settles the argument.

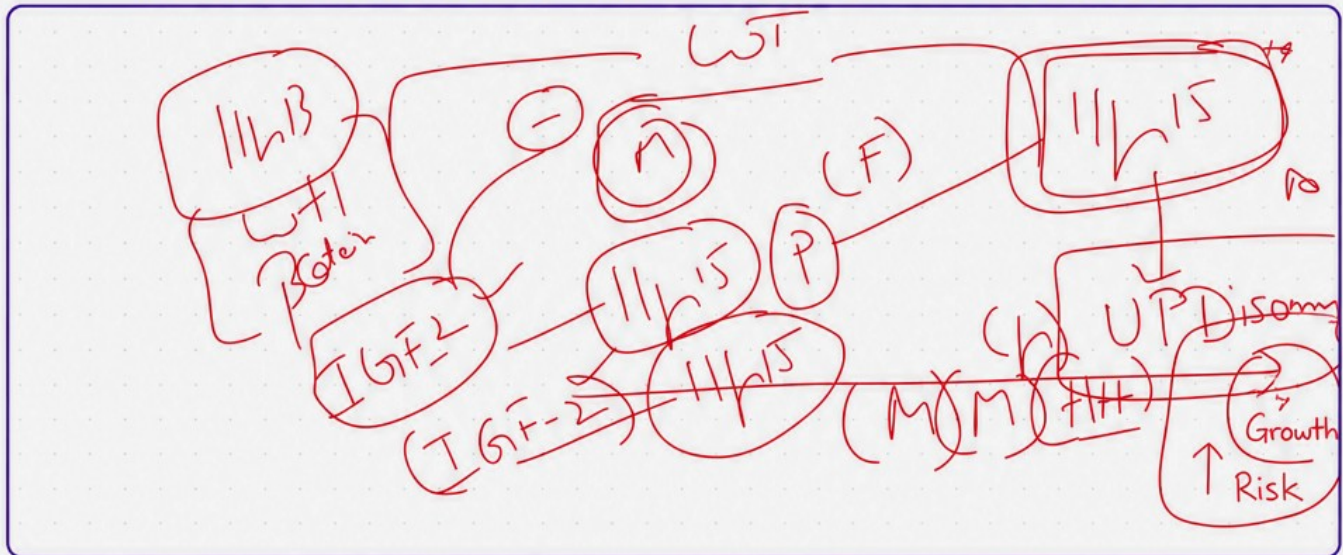


eLearning  
**FRCPATH**  
Master Pathology. One Concept at a Time

WHAT YOU ARE **NOT**  
READING AND THEY  
ARE NOT TELLING YOU

#Pathology  
ThatSticks

# WILMS TUMOR PATHOGENESIS FOCUS



## THE 2 MAJOR GENETIC PATHWAYS

### 11p13 PATHWAY



- Germline mutation in **WT1** gene
- May involve β-catenin (**CTNNB1**)



**Developmental arrest**  
(Intralobar nephrogenic rests)

### 11p15 PATHWAY



- Driven by Paternal Uniparental Disomy (**pUPD**)
- Both copies of 11p15 come from the father



**Overgrowth signal**  
(Perilobar nephrogenic rests)



Two different problems,  
one common outcome:

**Persistent nephrogenic  
progenitors → Wilms tumor**

Two completely different genetic wrong turns, same destination. Nephrogenic rests really don't like being told to stop growing.

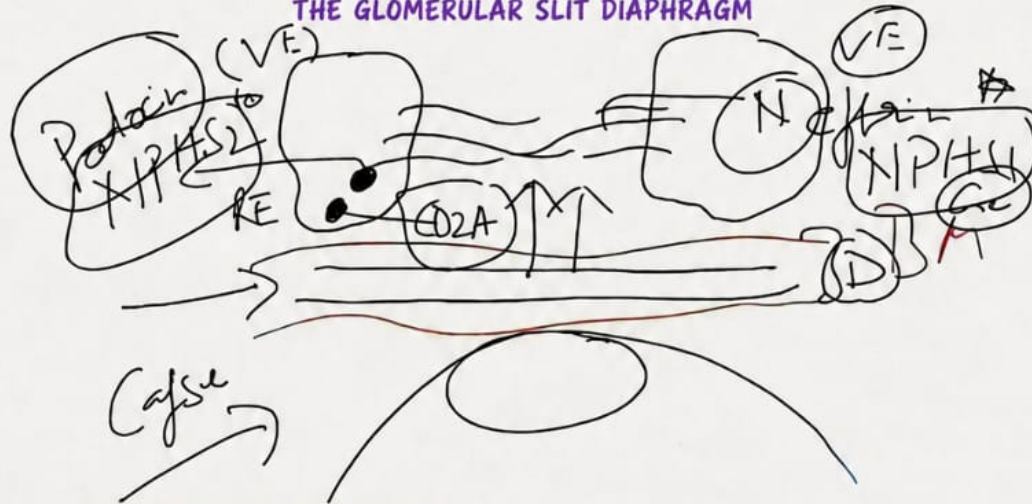


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WHAT YOU ARE NOT READING  
AND THEY ARE NOT TELLING YOU

# THE FILTER THAT KEEPS PROTEIN OUT

THE GLOMERULAR SLIT DIAPHRAGM



## THE DREAM TEAM OF THE FILTRATION BARRIER

### NEPHRIN

(GENE: NPHS1)

The main gatekeeper.  
Controls the filtration of  
albumin and other proteins.



### PODOCIN

(GENE: NPHS2)

The supporter.  
Lives inside the podocyte  
foot processes and  
connects directly to  
nephrin.



### CD2AP

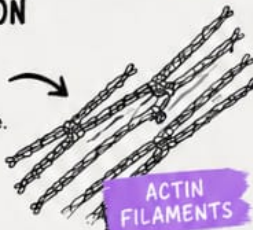
(GENE: CD2A)

The connector.  
Brings structure and  
stability to the slit  
diaphragm.



## THE POWER CONNECTION

- These proteins link up with **actin filaments** (the cell's skeleton) inside the podocyte.
- This gives strength, shape, and protection to the filtration barrier.



## WHEN THE CODE BREAKS



Mutations in NPHS1 or NPHS2  
disrupt this framework.



### RESULT?

COMPROMISED FILTRATION BARRIER  
→ PROTEIN LEAK → FSGS &  
CONGENITAL NEPHROTIC SYNDROME



### REMEMBER:

Tiny proteins.  
Big impact.  
Life-long consequences.

### UPCOMING CLASS

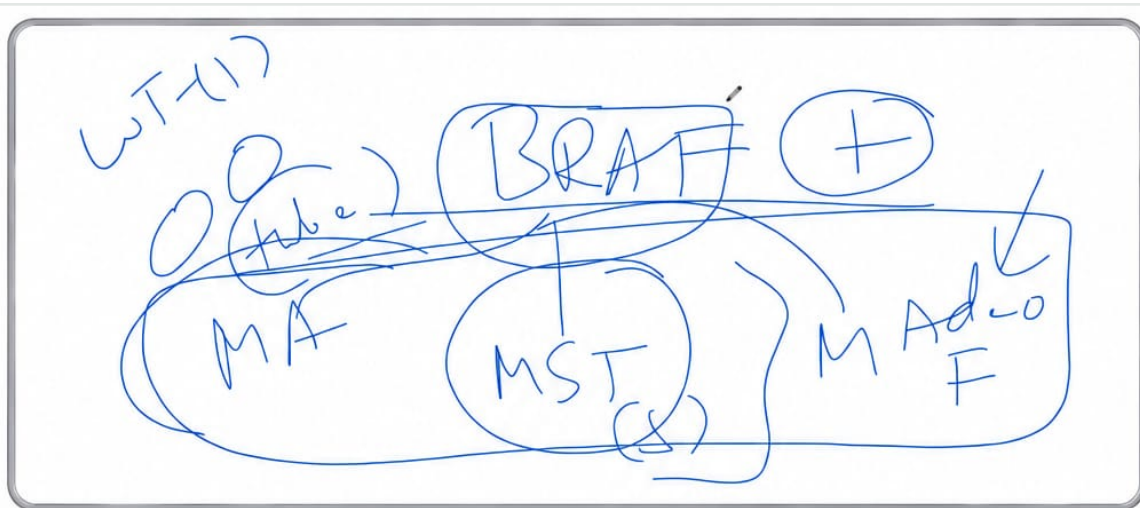
### MEDICAL KIDNEY DISEASE

Don't miss it!  
Save the date & level up!



STUDY SMART. THINK DEEP. STAY CURIOUS.

Nephrin, podocin and CD2AP hold the whole filtration barrier together. Break one, and the protein just walks straight out.



# BRAF-POSITIVE METANEPHRIC TUMORS



THE "BROTHERHOOD" OF THE KIDNEY 🤝

LEARN. VISUALIZE. EXCEL.

**THREE TUMORS. ONE GENE. DIFFERENT VIBES....**

GEN Z EDITION

They may look different, but **BRAF+** is their flex.

## 1 METANEPHRIC ADENOMA (MA)

- Morphology: Small tubules
- IHC: WT-1 positive
- BRAF is the real MVP
- Diagnosis flex: Highly specific with BRAF



**PROGNOSIS:  
EXCELLENT**

## 2 METANEPHRIC STROMAL TUMOR (MST)

- Morphology: Spindle cells
- Distinct but still in the crew
- BRAF+ keeps it in the family
- Indolent & chill (aka excellent prognosis)



**PROGNOSIS:  
EXCELLENT**

## 3 METANEPHRIC ADENOFIBROMA (MAAdF)

- Morphology: Unique glandular + stromal mix
- Different look, same BRAF+ story
- Still part of the metanephric fam



**PROGNOSIS:  
EXCELLENT**



## THE BIGGER PICTURE

Different morphologies. Same BRAF-driven pathway.

Diagnosis = Morphology + BRAF IHC. Easy. ✓



**SAME GENE  
DIFFERENT  
DRIP**

## KEY TAKEAWAYS FOR GEN Z PATHOLOGY

- ✓ Know the 3 brothers: MA, MST, MAAdF
- ✓ BRAF+ is the glue that holds them together
- ✓ Excellent prognosis = good vibes only
- ✓ Morphology is the look, BRAF is the hook 🔥

## STUDY SMART, NOT HARD.

Understand the story.

Crush the exam. ⚡



**eLearningFRCPath**

THREE TUMORS. ONE GENE. DIFFERENT VIBES.... | BRAF+ = THE FLEX 💪

Three tumors, three completely different looks, one shared BRAF mutation running the show backstage.

## Side by Side: Congenital Mesoblastic Nephroma

WHAT YOU. are **NOT** READING!  
They didn't tell you this in lectures. We did.

SAVE THIS!

HIGH YIELD INFO

Classical CMN

EGFR ITD

ETV6-NTRK

SCN SC S TF

CMN

Rn TRK IHC

Point (NSCLC ADAR)

**CONGENITAL MESOBLASTIC NEPHROMA (CMN)**  
**IT'S NOT ALL THE SAME!**

Two subtypes. Two genetic drivers. Very different recurrence risk.

**CLASSICAL CMN**  
DRIVER: **EGFR ITD** (Internal Tandem Duplication)  
I'M CHILL  
✓ Classical subtype  
✓ Usually **INDOLENT**  
✓ **LOW** recurrence risk  
✓ Think: EGFR ITD  
BEHAVES: **BENIGN**

**CELLULAR CMN**  
DRIVER: **ETV6-NTRK** (Gene Fusion)  
HIGH RISK OF COMING BACK  
✓ Cellular subtype  
✓ Usually **INDOLENT** overall BUT  
✓ **HIGH** recurrence risk  
✓ Think: ETV6-NTRK  
BEHAVES: **HIGH RECURRENCE**

Same tumor name, two very different personalities.  
One's chill. The other one keeps coming back.

VS

**THE POOR COUSIN?  
NO. THE MORPHOLOGIC TWIN!**  
Cellular CMN and Infantile Fibrosarcoma – Same Story, Different Address.

Child < 1 year

IF

Sarcoma

CMN

cellular congenital ETV6-NTRK3

ETV6-NTRK3 ✓

**WHAT YOU ARE NOT READING AND THEY ARE NOT TELLING YOU**

BEYOND THE TEXTBOOK.

BEYOND THE SLIDES.

REAL INSIGHTS THAT MAKE YOU EXAM-READY.

**NEETSS PATHOLOGY EXAM DATE ANNOUNCED!**  
**11 & 12 DEC 2026**  
Mark the Dates. Plan Your Success!

**WHAT YOU MUST KNOW**

SHARED GENETIC MUTATION  
t(12;15)(p13;q25)  
ETV6-NTRK3 fusion

MORPHOLOGICALLY IDENTICAL  
Under the microscope, they are indistinguishable.

DIFFERENT ADDRESSES  
• IF: Soft tissues  
• CMN: Kidney

PAN-TRK IHC SURROGATE MARKER  
A powerful tool to identify both entities.

MORPHOLOGY ALONE CAN MISLEAD.  
MOLECULAR PATHOLOGY REVEALS THE TRUTH.

START YOUR PREPARATION WITH **eLearningFRCPath**  
**NEETSS PATHOLOGY COURSE**

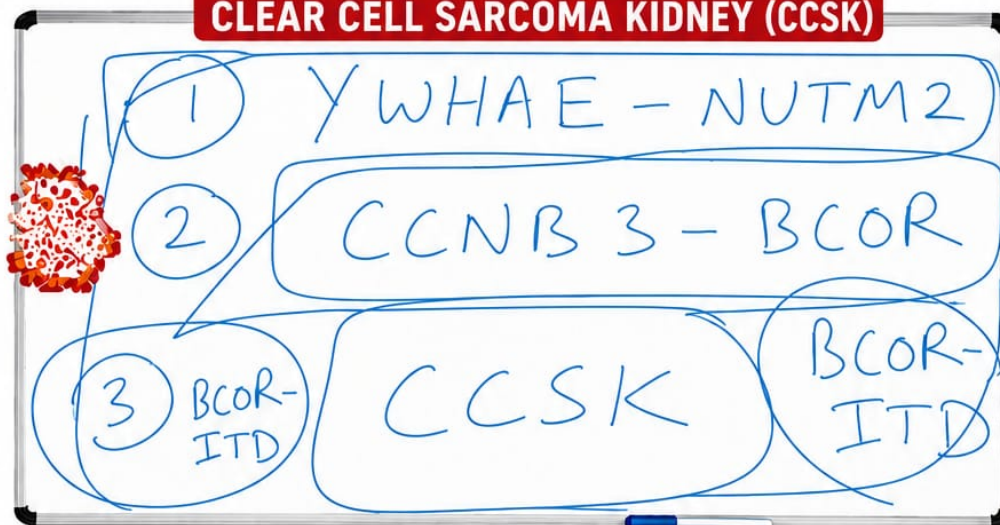
HIGH YIELD CONCEPTS  
INTEGRATED APPROACH  
EXAM FOCUSED PREPARATION  
EXPERT GUIDANCE  
RESULT DRIVEN

Identical under the microscope, same fusion gene,  
different postcode. Morphology alone would never  
have caught this.

Same name, different personalities — and the exam knows it.

# ❖ PEDIATRIC RENAL TUMORS ❖

## MOLECULAR PATHOBIOLOGY FOR CLEAR CELL SARCOMA KIDNEY (CCSK)



**WHAT YOU ARE **NOT** READING  
AND THEY ARE **NOT** TELLING YOU.**

ONE FAMILY. **THREE HITS**. **MUTUALLY EXCLUSIVE**.

**1**  
**BCOR-ITD**  
(INTERNAL TANDEM  
DUPLICATION)  
  
MOST COMMON ALTERATION  
IN CCSK

**2**  
**YWHAE-NUTM2**  
FUSION  
  
SPECIFIC CHROMOSOMAL  
TRANSLOCATION

**3**  
**CCNB3-BCOR**  
FUSION  
  
DISTINCT MOLECULAR  
VARIANT



### CROSSOVER INTO GYNECO-PATH

High-grade Endometrial Stromal Sarcomas (ESS) are frequently defined by the same molecular signatures (YWHAE fusions and BCOR alterations).



### BONE & SOFT TISSUE CONNECTION

Tumors with CCNB3-BCOR fusion are now recognized as a distinct disease entity – not just “round cell sarcoma” anymore.



### THE GOLDEN RULE:

THESE 3 ALTERATIONS ARE **MUTUALLY EXCLUSIVE**.  
IF A TUMOR HAS **ONE**, IT WON'T HAVE THE OTHER TWO.

**elearningfrcpath**

 DEEP LEARNING. | REAL UNDERSTANDING. | EXAM DOMINANCE.



NEETSS PATHOLOGY EXAM

**DEC 11<sup>TH</sup>**

YOUR D-DAY. OWN IT.

PATHOLOGY THAT MAKES SENSE. | **CONCEPTS THAT STICK.** | RANKERS TRUST US. 

One family of mutations, three members, and a strict no-overlap policy. CCSK does not do combos.

## (A) CLEAR CYTOLOGY

Cells look clear (glycogen/lipid)



- ✓ ELOC-mutated RCC
- ✓ TFE3 rearranged RCC
- ✓ TFE3 rearranged RCC
- ✓ mTOR-mutated RCC

### DIFFERENTIAL DX

- Clear cell RCC
- Chromophobe RCC
- Clear cell papillary renal tumor (CCPRT)

## (C) PAPILLARY PATTERN

Tubulopapillary / papillary structures



- ✓ FH-deficient RCC
- ✓ TFE3 amplified RCC
- ✓ TFE3 rearranged RCC
- ✓ ALK rearranged RCC

### DIFFERENTIAL DX

- Papillary RCC
- MTSCC (mucinous tubular & spindle cell carcinoma)

## (B) EOSINOPHILIC CYTOLOGY

Cells look pink (mitochondria rich)



- ✓ SDH-deficient RCC
- ✓ FH-deficient RCC

### DIFFERENTIAL DX

- Renal oncocytoma
- Eosinophilic chromophobe RCC
- Low-grade oncocytic tumor (LOT)
- Other oncocytic tumors (e.g., EVT)

## (D) INFILTRATIVE PATTERN

Infiltrative / destructive growth

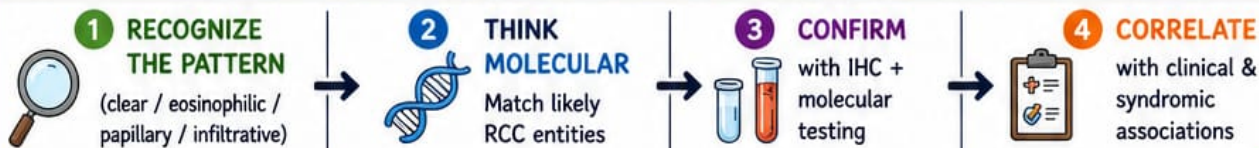


- ✓ SMARCB1-deficient renal medullary carcinoma
- ✓ ALK rearranged RCC

### DIFFERENTIAL DX

- Urothelial carcinoma
- NF2-mutated RCC
- Collecting duct carcinoma
- Metastasis

## THE GAME PLAN — MORPHOLOGY GUIDES YOU, MOLECULAR CONFIRMS IT!



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Pathology Learning **Simplified**. Exam Success **Amplified**.

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Thousands of  
Pathology  
Aspirants

Clear, pink, papillary or invasive — the cytoplasm hands you the first clue before molecular testing even opens its mouth.

# WHAT YOU ARE NOT READING AND THEY ARE NOT TELLING YOU

## SERIES

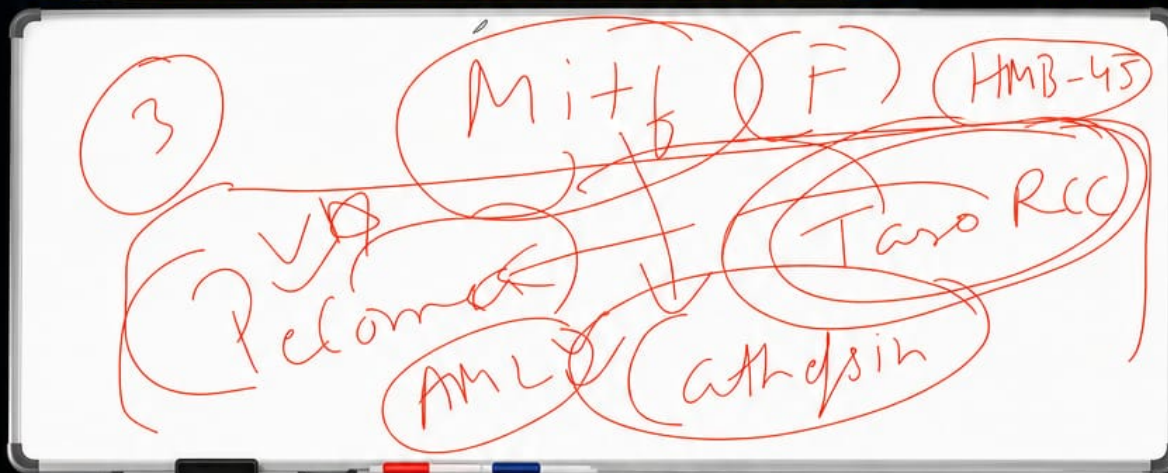


eLearning

# FRCPath

High-Yield Pathology Learning

## THE REAL STORY BEHIND MITF FAMILY RCC, PEComas, CATHEPSINS & HMB45



### EXAM FACTS

- ✓ MIT/TFE PATHWAY
- ✓ LYSOSOMES
- ✓ MELANOSOMES
- ✓ CATHEPSIN K
- ✓ HMB45

### HIGH-YIELD!

## THE MIT/TFE – LYSOSOME – MELANOSOME AXIS

### 1. MIT/TFE ACTIVATION



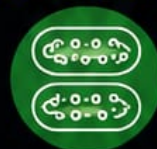
- Translocation / mutation / amplification / mTOR dysregulation (TSC1/2 loss)
- → **Constitutive nuclear activation**

### 2. LYSOSOMAL EXPANSION



- CLEAR network upregulation
- Lysosomal biogenesis, autophagy, trafficking
- ↑ **Cathepsins** (Cathepsin K, L, B)

### 3. MELANOSOME-RELATED PROGRAM



- Melanosomes are lysosome-related organelles (LROs)
- ↑ PMEL (gp100), TYR, MART1, Melan-A
- → **HMB45** positivity

### 4. TUMOR PHENOTYPE



- Eosinophilic, granular cytoplasm
- Nested / alveolar patterns
- Co-expression of **Cathepsin K + HMB45** ± Melan-A

### 5. mTOR / TSC CONNECTION



- TSC1/2 loss → mTOR activation
- TFEB/TFE3 escape cytoplasmic retention
- Translocate to nucleus → program **ON**

### WHERE YOU SEE THIS AXIS



**PEComas**  
(AML, LAM, PComa NOS)



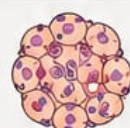
**TFEB-rearranged RCC**



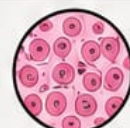
**TFE3-rearranged RCC**



**Epithelioid Angiomyolipoma (AML)**



**Eosinophilic Vacuolated Tumors (TSC)**



**Eosinophilic Solid & Cystic RCC**

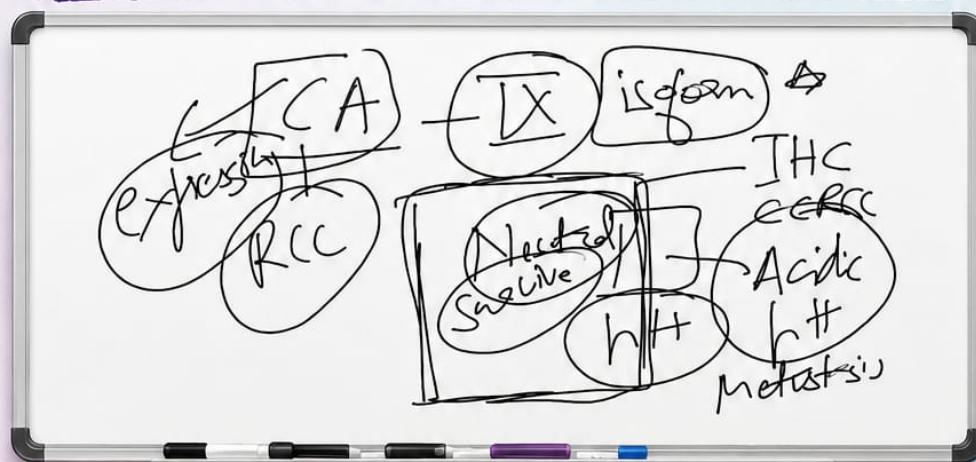


**Other mTOR/TSC-associated Eosinophilic Renal Tumors**

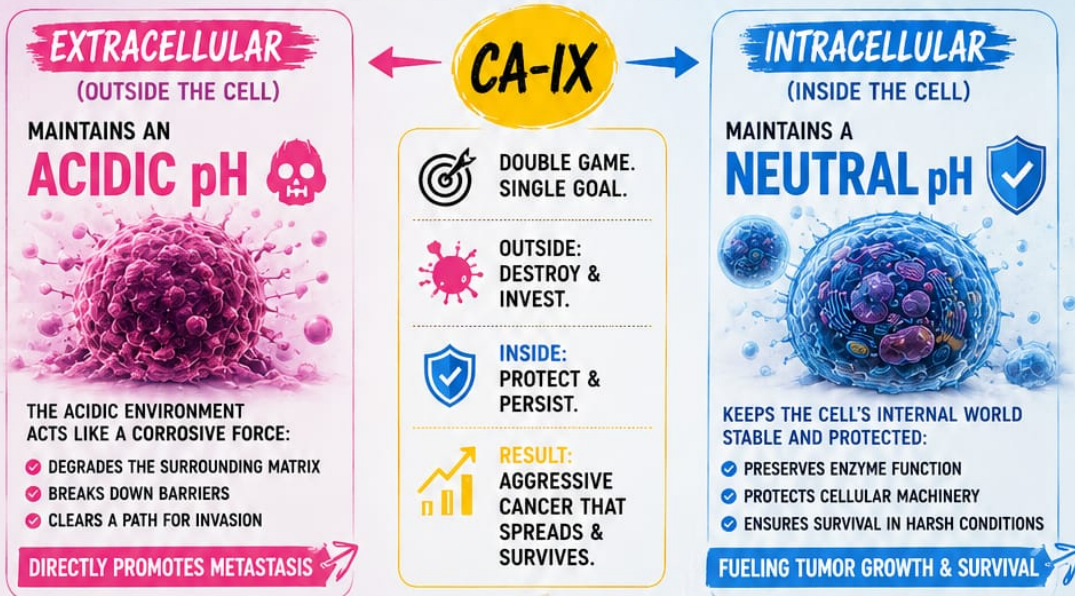
**DIFFERENT NAMES. SAME BIOLOGIC PROGRAM.**

PEComas, TFE3-rearranged RCC and HMB45 positivity all trace back to the same lysosome-melanosome program. Small world.

# WHAT YOU ARE NOT READING AND THEY ARE **NOT** TELLING YOU IS.....



THE NORMAL JOB OF CARBONIC ANHYDRASE (CA) IS TO MAINTAIN pH. BUT IN CARCINOMA CELLS—ESPECIALLY RCC—IT FLIPS THE SCRIPT TO HELP TUMORS GROW, SURVIVE, AND SPREAD.



CA-IX is not just a marker. It's a master switch in RCC. Target it. Understand it. **Disrupt it.** That's how we stop it.

KNOWLEDGE IS **POWER**. QUESTION MORE. LEARN DEEPER.



STAY CURIOUS. STAY AHEAD. YOUR NEXT DISCOVERY COULD **SAVE LIVES**.

elearning **FRC** PATH

LEARN BEYOND. LEAD BEYOND.



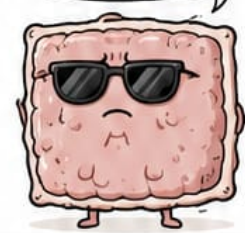
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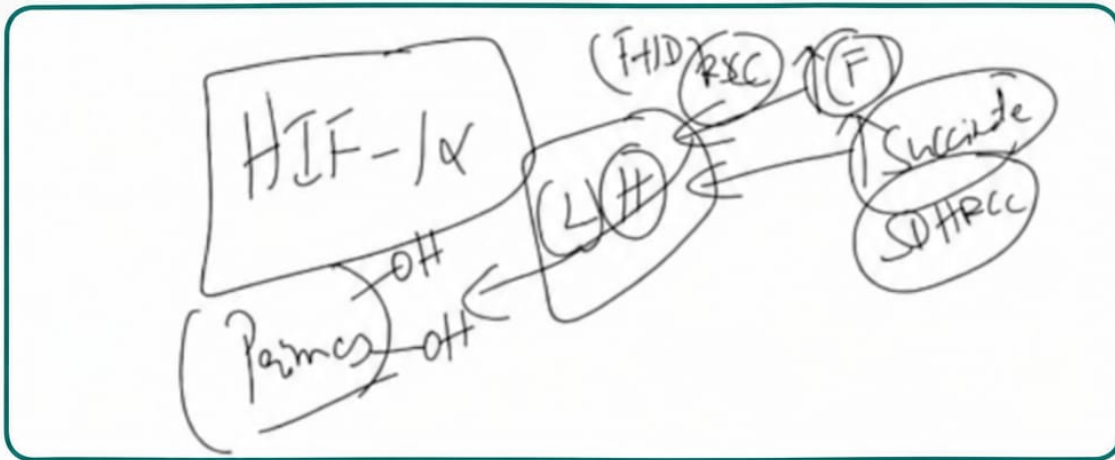
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#LearnBeyondLeadBeyond

Carbonic anhydrase's day job is keeping pH balanced. In renal cell carcinoma, it moonlights as a metastasis enabler.

| <div>  <b>eLearning FRCPath™</b><br/> Your Path. Our Purpose. ❤️👉 </div>                                                                                                                                                                                                        |                                                                                                                                        |                                                                                                                                            |                                                                                                                                               |                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <div> <div>  <p>Different looks.<br/>Different vibes!</p> </div> <div> <b>EOSINOPHILIC RENAL TUMORS</b><br/> <b>WHO'S WHO?</b> </div> <div>  <p>Know me,<br/>Don't mix me!</p> </div> </div> |                                                                                                                                        |                                                                                                                                            |                                                                                                                                               |                                                                                                                                       |
|                                                                                                                                                                                                                                                                                                                                                                  | <b>LOT</b><br>(Low-grade Oncocytic Tumor)                                                                                              | <b>ONCOCYTOMA</b>                                                                                                                          | <b>CHROMOPHOBE RCC</b>                                                                                                                        | <b>EVT</b><br>(Eosinophilic Vacuolated Tumor)                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                  | <p>I'm chill &amp; low-grade. CK7 yes, CD117 no!</p>  | <p>I'm benign &amp; classic. CD117 is my superpower!</p>  | <p>I've got plant cell borders &amp; raisinoid nuclei!</p>  | <p>I'm vacuolated &amp; on the mTOR spectrum!</p>  |
|  ARCHITECTURE                                                                                                                                                                                                                                                                 | Solid / Nested                                                                                                                         | Nested / Tubular                                                                                                                           | Solid sheets                                                                                                                                  | Solid nests                                                                                                                           |
|  CYTOPLASM                                                                                                                                                                                                                                                                    | Eosinophilic                                                                                                                           | Dense granular oncocytic                                                                                                                   | Pale eosinophilic with perinuclear halos                                                                                                      | Eosinophilic with prominent vacuoles                                                                                                  |
|  NUCLEI                                                                                                                                                                                                                                                                       | Bland, low-grade                                                                                                                       | Round, uniform                                                                                                                             | Irregular "raisinoid"                                                                                                                         | Large nucleoli common                                                                                                                 |
|  CLUE                                                                                                                                                                                                                                                                         | Hybrid LOT phenotype                                                                                                                   | Central scar (gross)                                                                                                                       | Wrinkled nuclei + halos                                                                                                                       | Intracytoplasmic vacuoles                                                                                                             |
|  CK7                                                                                                                                                                                                                                                                          | <b>POSITIVE</b><br>(diffuse)                                                                                                           | <b>NEGATIVE / Focal</b>                                                                                                                    | <b>POSITIVE</b><br>(diffuse)                                                                                                                  | <b>FOCAL / PATCHY</b>                                                                                                                 |
|  CD117 (KIT)                                                                                                                                                                                                                                                                  | <b>NEGATIVE</b>                                                                                                                        | <b>POSITIVE</b>                                                                                                                            | <b>POSITIVE</b>                                                                                                                               | <b>POSITIVE</b>                                                                                                                       |

Four pink, granular tumors that all deserve their own name instead of one shared shrug.



## MECHANISM OF HIF-1α REGULATION

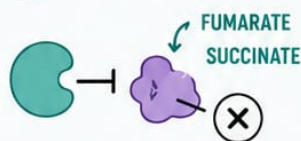
**HIGH-YIELD**  
**MADE SIMPLE** 💡

### 1 HYDROXYLATION



The enzyme **prolyl hydroxylase** adds a hydroxyl group (**-OH**) to HIF-1α, priming it for degradation.

### 2 INHIBITION



This hydroxylase enzyme is inhibited by high cellular levels of **fumarate** or **succinate**.

### 3 EFFECT



Inhibition prevents hydroxylation, leading to **HIF-1α** stabilization and activation of genes that drive tumorigenesis.

### ⚠️ PATHOLOGICAL IMPLICATIONS

The accumulation of these metabolites due to enzyme deficiencies leads to specific cancers:

#### FH DEFICIENCY



**Fumarate Hydratase (FH) Deficiency:**  
Causes fumarate to accumulate, leading to Fumarate Hydratase-deficient RCC (**FH-RCC**).

#### SDH DEFICIENCY



**Succinate Dehydrogenase (SDH) Deficiency:**  
A similar mechanism where **succinate accumulation** inhibits the hydroxylase, contributing to tumorigenesis (often associated with hereditary paraganglioma-pheochromocytoma syndromes).



**FOCUS.  
LEARN.  
ACE FRCPath.**



Trusted by Pathology Aspirants  
for **FRCPath & NEET SS**



SCAN TO  
**LEARN MORE!**

*Block the hydroxylase, stabilize HIF-1α, and the tumorigenesis switch flips before anyone notices.*

# 09

## GASTROINTESTINAL PATHOLOGY

---

*Colon cancer's favorite tricks, and the syndrome you should never miss.*

5 panels • maps to:

NEET-SS Pathology

FRCPATH Part 1

# TINY BUDS, BIG SIGNALS

elearning  
FRCPath 

Small Cells.  
Big Clues.  
Stronger Decisions.

## TUMOR BUDDING IN CRC



### WHAT IS TUMOR BUDDING?

Presence of single tumor cells or small clusters of fewer than 5 cells (usually 1–4 cells) at the advancing front of colorectal carcinoma.

### WHY IT MATTERS



#### POOR PROGNOSIS

Established indicator of poor outcomes in CRC & other solid tumors.



#### HIGHER METASTASIS RISK

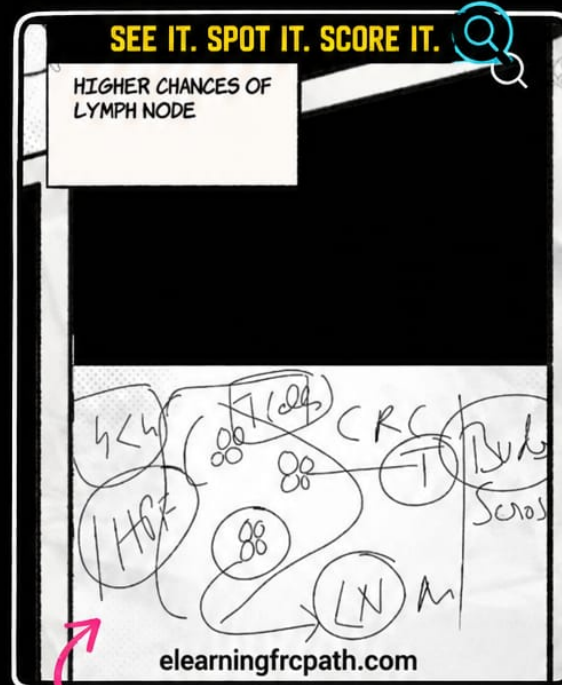
Higher degree of budding = higher risk of lymph node metastasis.



#### QUANTIFIABLE & ACTIONABLE

Count buds per high-power field (HPF) and grade:

1–5 | >5 | >10 buds



Screenshot from our quick explainer  
(simple sketch, powerful message!)

### VISUAL CONTEXT



Serosa  
Outer layer of intestine



Advancing Front  
The leading edge of the tumor



Buds  
Small clusters (1–4 cells) breaking away



### CLINICAL TAKEAWAY

Tumor budding reflects epithelial-mesenchymal transition (EMT) – a sign of aggressive behavior. Spotting these tiny buds today can **change the treatment strategy tomorrow.**

**SMALL BUDS.  
STRONGER  
FORECAST.  
BETTER CARE.**



### REMEMBER:

Count. Grade. Guide.  
Better pathology. Better outcomes.

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Learn **Smart**. Score **High**. Impact **Lives**.



@elearningfrcpath

One to four cells breaking off at the invasive front. Small detail, huge difference to the prognosis line of the report.

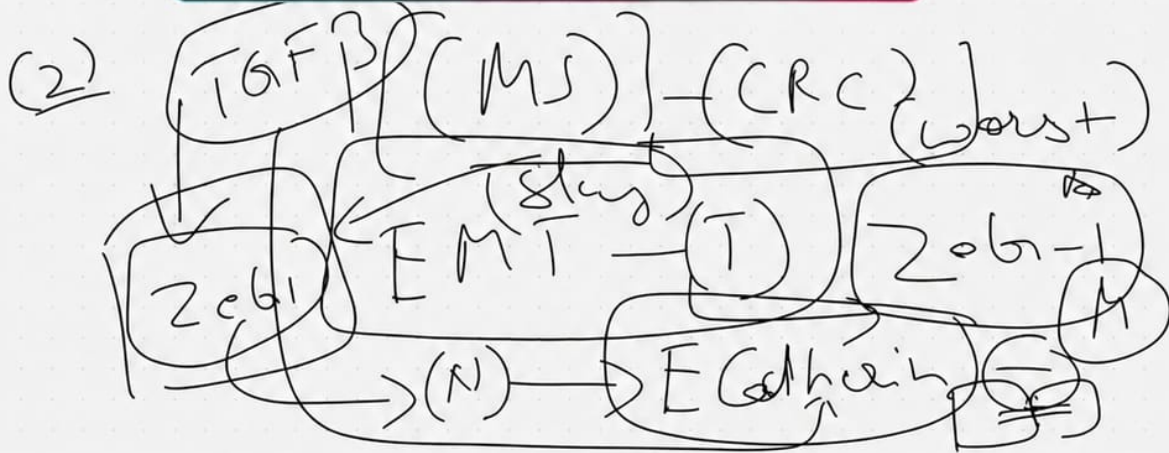


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High-Yield Learning  
Exam-Focused  
Visual. Structured. Effective.

### WHITEBOARD SCREENSHOT (ORIGINAL)



## CRC MOLECULAR SUBTYPES & PROGNOSIS



### MESENCHYMAL SUBTYPE

= CMS4

- Characterized by prominent **EMT**
- **Worst prognosis** among CRC subtypes

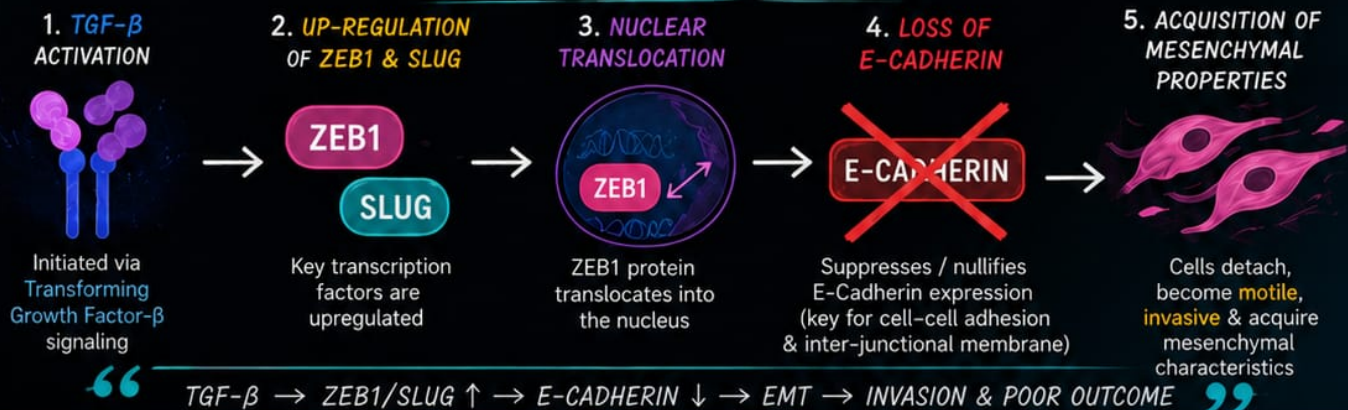


### BEST PROGNOSIS SUBTYPE

= CMS2

- Typically APC-mutated
- Epithelial / Canonical
- Much more **favorable prognosis**

### THE TGF-β / EMT PATHWAY



Same organ, same word "colorectal," wildly different outcomes depending on which CMS subtype shows up.

**SNAIL?**  **SLUG?** 

**ZEB1?**  **GLUT1?** 

WHAT IS THIS GEN Z LANGUAGE...

NO! THIS IS ABOUT THE **PATHOGENESIS** OF

# COLON CANCER

CRACK THE CODE. **BEAT THE DISEASE.**

SESSION ON  
**GIT TUMORS**

FOR NEETSSPATHOLOGY/  
FRCPATH PART 1

## GEN Z LANGUAGE



### SNAIL

= EMT ACTIVATOR  
(KICKSTARTS  
INVASION)



### SLUG

= EMT BOOSTER  
(DRIVES  
MIGRATION)



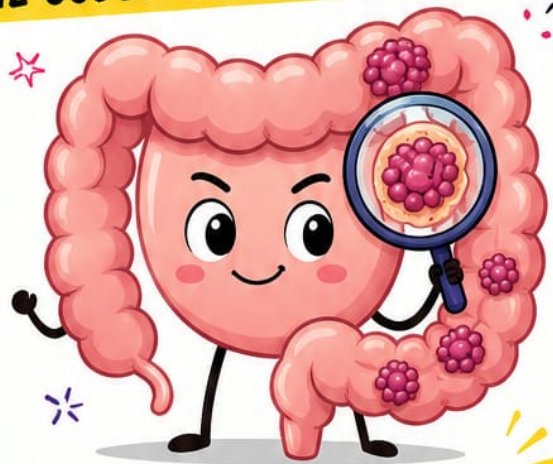
### ZEB1

= TRANSCRIPTION  
REPRESSOR,  
METASTASIS BOSS!



### GLUT1

= GLUCOSE UPTAKE,  
TURBO MODE!



HIGH YIELD  
PATHOGENESIS



NEETSSPATHOLOGY/  
FRCPATH PART 1  
FOCUSED



CONCEPTUAL  
CLARITY



NEXT LEVEL  
PREPARATION

PART 1



**6PM  
TODAY**



INDIA TIME

DON'T JUST  
STUDY.  
UNDERSTAND.  
**DOMINATE!**



**ELEARNINGFRCPATH**

LEARN • UNDERSTAND • CONQUER

Snail, Slug and ZEB1 sound like a band lineup. They're actually why colon cancer cells learn to let go and invade.

# ★ LYNCH SYNDROME

aka **HNPCC** THINK EARLY. THINK FAMILIES. THINK LYNCH.

**HIGH  
YIELD  
ALERT!**

**1**

## AGE-BASED SCREENING

Any patient diagnosed with **COLORECTAL CARCINOMA (CRC)** before the age of

**50**

should be investigated for **HNPCC**.



## GEN Z NOTE

**YOUNG AGE  
+ CRC  
= CHECK FOR  
LYNCH!**



**2**

## HISTOLOGICAL FEATURES IN PATIENTS **UNDER 60**

Certain patterns in colorectal tumors strongly suggest **HNPCC**.



### SIGNET-RING MORPHOLOGY



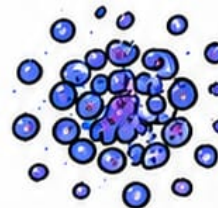
Cells that resemble a signet ring due to a large **mucus vacuole**.

### MUCINOUS MORPHOLOGY



A tumor that produces significant amounts of extracellular **mucus**.

### LYMPHOCYTIC REACTION



Specifically, a **Crohn's-like** reaction, where lymphoid aggregates are present at the tumor's advancing edge.

*Colorectal cancer before 50 isn't bad luck until someone proves otherwise. Check for Lynch first.*

# PDGFRA MUTATIONS

## IN GIST PATIENTS

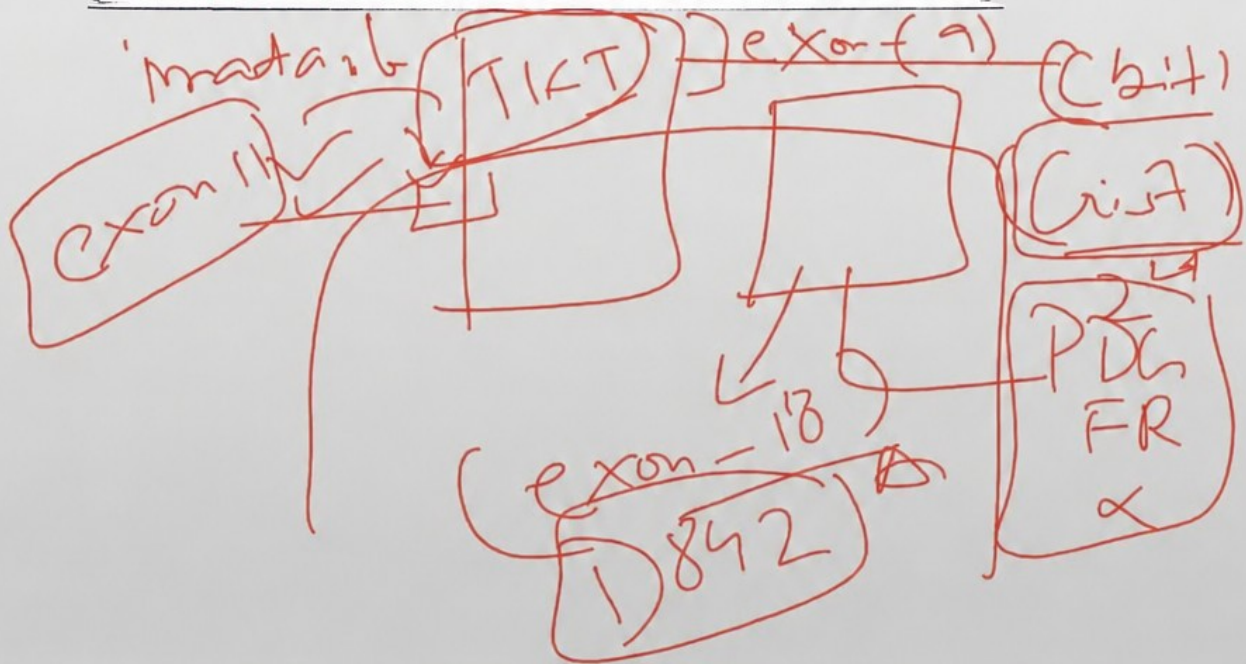


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LEARN  
TODAY  
LEAD  
TOMORROW

WHITEBOARD EXPLAINED BY ELEARNINGFRCPATH.COM



**PDGFRA** MUTATIONS DRIVE A DISTINCT SUBSET OF **GISTs** — KNOW THEM, TARGET THEM!



### WHERE DO THEY OCCUR?

- Predominantly in exon 18 of PDGFRA gene
- Key hotspot: **D842V** mutation



### COMMON PDGFRA MUTATIONS

- D842V (Exon 18) – most common
- D842Y (Exon 18)
- D842H (Exon 18)



### IMATINIB RESPONSE



D842V mutation is **RESISTANT** to Imatinib

Exon 18's D842V mutation shrugs off imatinib like it's nothing. Know this one before the exam does.

# 10

## BONUS: IMMUNO-ONCOLOGY & ABOUT ELEARNING FRCPATH

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*One last high-yield concept, then meet the people behind this book.*

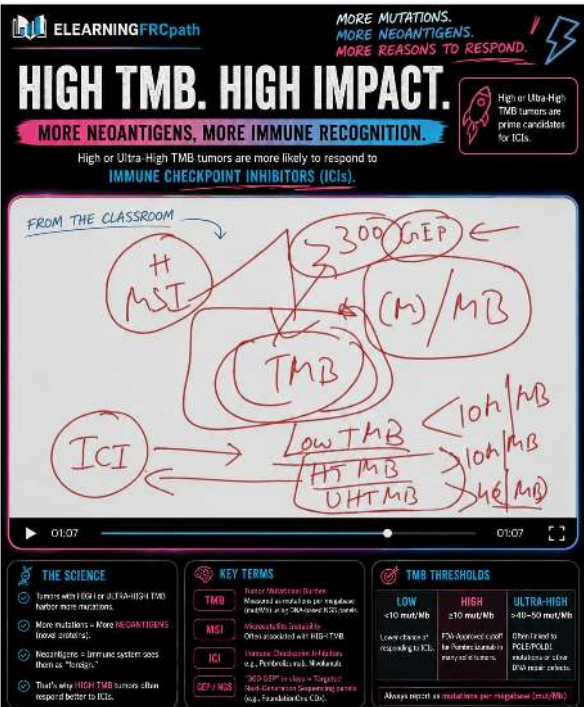
2 panels • maps to:

FRCPATH Part 1

FRCPATH Part 2

NEET-SS Pathology

## Closing Spread



**THE SCIENCE**

- Tumors with ICI for ultra-high TMB harbor more mutations.
- More mutations = More NEOANTIGENS = more reasons.
- Neoantigens = immune system sees them as "foreign".
- That's why HIGH TMB tumors often respond better to ICIs.

**KEY TERMS**

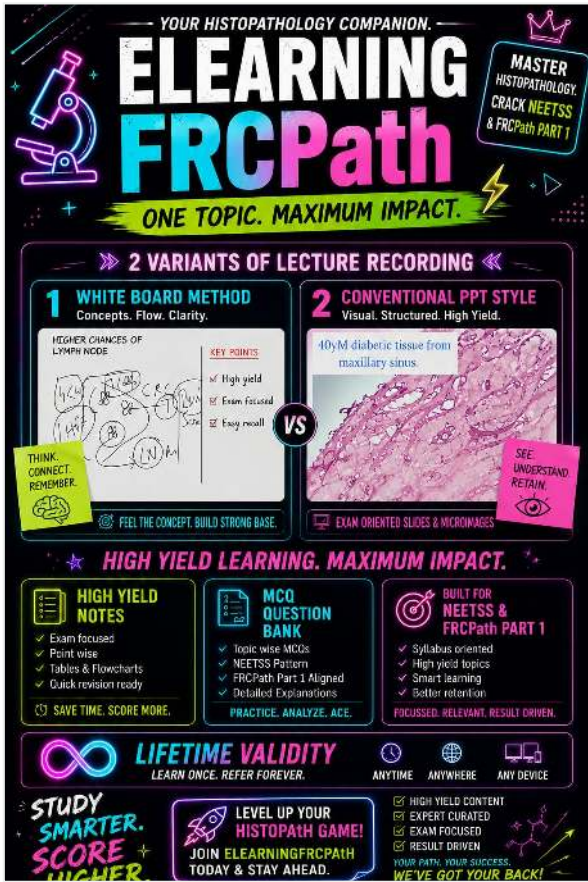
- TMB**: Tumor Mutational Burden. Measured as mutated bases per megabase (mut/Mb) or as % mutated bases.
- MSI**: Microsatellite Instability. Often associated with high TMB.
- ICI**: Immune Checkpoint Inhibitors. e.g., Pembrolizumab, Nivolumab.
- GEP / MSI**: 300 GEP in class = Targeted Anti-Cancer Therapy. See: Translational Q&A.

**TMB THRESHOLDS**

| LOW                                | HIGH                                                         | ULTRA-HIGH                                                        |
|------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------|
| <10 mut/Mb                         | ≥10 mut/Mb                                                   | >40-50 mut/Mb                                                     |
| Lower chance of responding to ICI. | ICI Associated Conf. for Pembrolizumab in many solid tumors. | Often linked to POLE/POLD1 mutations or other DNA repair defects. |

*Always report as mutations per megabase (mut/Mb).*

→



**2 VARIANTS OF LECTURE RECORDING**

**1 WHITE BOARD METHOD**  
Concepts. Flow. Clarity.

HIGHER CHANCES OF LYMPH NODE

KEY POINTS

- ✓ High yield
- ✓ Exam focused
- ✓ Easy recall

THINK. CONNECT. REMEMBER.

FEEL THE CONCEPT. BUILD STRONG BASE.

**2 CONVENTIONAL PPT STYLE**  
Visual. Structured. High Yield.

40yM diabetic tissue from maxillary sinus.

VS

SEE. UNDERSTAND. RETAIN.

EXAM ORIENTED SLIDES & MICROIMAGES

**HIGH YIELD LEARNING. MAXIMUM IMPACT.**

**HIGH YIELD NOTES**

- ✓ Exam focused
- ✓ Point wise
- ✓ Tables & Flowcharts
- ✓ Quick revision ready

SAVE TIME. SCORE MORE.

**MCQ QUESTION BANK**

- ✓ Topic wise MCQs
- ✓ NEETSS Pattern
- ✓ FRCPath Part 1 Aligned
- ✓ Detailed Explanations

PRACTICE. ANALYZE. ACE.

**BUILT FOR NEETSS & FRCPath PART 1**

- ✓ Syllabus oriented
- ✓ High yield topics
- ✓ Smart learning
- ✓ Better retention

FOCUSSED. RELEVANT. RESULT DRIVEN.

**LIFETIME VALIDITY**  
LEARN ONCE. REFER FOREVER.

ANYTIME ANYWHERE ANY DEVICE

**STUDY SMARTER. SCORE HIGHER.**

**LEVEL UP YOUR HISTOPATH GAME!**  
JOIN ELEARNINGFRCPath TODAY & STAY AHEAD.

- ✓ HIGH YIELD CONTENT
- ✓ EXPERT CURATED
- ✓ EXAM FOCUSED
- ✓ RESULT DRIVEN

YOUR PATH. YOUR SUCCESS. WE'VE GOT YOUR BACK!

More mutations means more neoantigens means more reasons for the immune system to finally notice the tumor.

Messy whiteboard or clean slide deck — however it clicks for you, the goal's the same: walk into that exam and actually know it.

*That's a wrap. Now go make those 70 panels count.*



# Liked the Panels? Wait Till You See the Courses.

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