# Practice Updates in Genitourinary Molecular Oncology: A Case Based Approach

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## Learning Objectives

- Outline the standard of care molecular testing practices in genitourinary tumors
- Provide an overview of molecular alterations seen in genitourinary tumors
- Discuss using case scenarios how pathologists can use molecular testing for
  - Purpose of diagnosis
  - Suggesting hereditary predisposition and testing
  - Integrate information in molecular tests into pathology reports

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## Outline

- Kidney tumors
  - Diagnostic biomarkers
  - Hereditary predisposition
- Bladder and Prostate
  - Histogenesis biomarkers- diagnostic
  - Germline and somatic testing for prostate cancer
- Testicular Tumors
  - Diagnostic biomarkers
- Penile carcinomas
  - Viral association
- Immunotherapy Biomarkers

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# Kidney

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## Case 1

- 37F, right flank pain
- Family History:
  - Paternal grandmother- Uterine and stomach carcinoma
  - Brother-leukemia
- Ultrasound- 5 cm renal mass with renal vein thrombus extending into inferior vena cava, intracaval lymph nodes
- Radical nephrectomy with retroperitoneal lymphadenectomy

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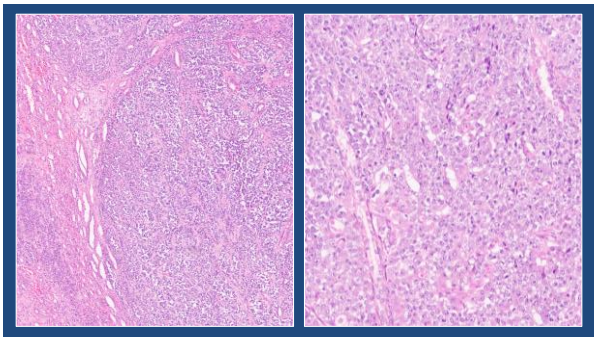

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## Case 1: IHC/ FISH

**Positive**

- CK7
- INI1
- SMARCA4
- CA-IX
- CK20 (focal)
- 34BE12 (focal)
- P63 (focal)
- PAX8 (focal)

**Negative**

- Vimentin
- GATA3
- UP
- PAX2
- RCC
- ALK
- OCT4
- SALL4
- ER
- TTF-1
- ER
- Synaptophysin
- Chromogranin
- WT-1
- SOX-10
- Desmin
- H3
- BCOR
- EWS
- FUS
- SYT, BCOR , YWHAE gene abnormalities

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## Case 1

- Poorly differentiated carcinoma, possibly of distal nephron origin, invading into renal vein
- pT3aN1
- Genetic testing: diagnostic or predictive biomarkers

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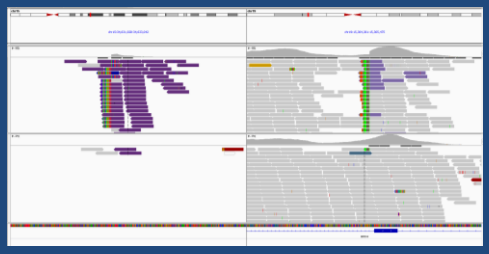

***BRD4-NUTM1* fusion** → ***NUT rearranged carcinoma***

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## 1 month later….

- Extensive hypermetabolic soft tissue/ LN in nephrectomy bed, retroperitoneum
- Multiple bilateral pulmonary nodules
- Extensive staging work up did not reveal any other primary
- GSK BET inhibitor
- Decrease in size of most target lesions with growth of non-target lesions in peritoneum.
- Immunotherapy
- DOD-6m

Sirohi D et al. Histopathology. 2018 Feb;72(3):528-530

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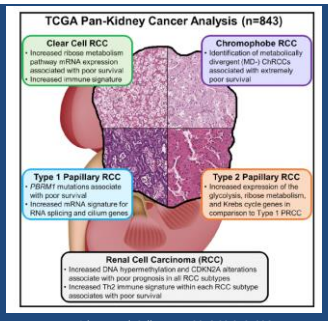


Ricketts et al. Cell Reports 2018;23:313–326

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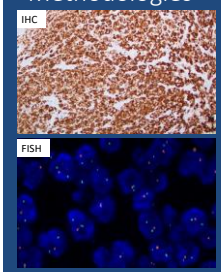
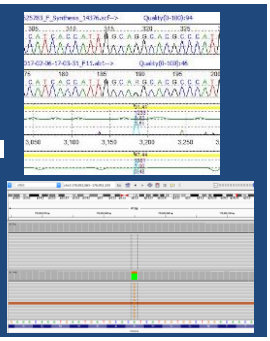
## Common Molecular Testing Methodologies




Sequencing



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| Tumor Type | Diagnostic Biomarkers | Testing Methodology |
|---|---|---|
| Clear Cell RCC | VHL, Loss of 3p<br>BAP1, SETD2, PBRM1 | Sequencing, FISH, methylation assays, chromosomal microarrays |
| Papillary RCC type 1 | Gains of chr 7, 17, loss of Y<br>MET | Sequencing, FISH, chromosomal microarrays |
| Chromophobe RCC | Loss of chr 1, 2, 6, 10, 13, and 17<br>TP53, PTEN, mTOR, FLCN | Sequencing, chromosomal microarrays |
| MIT Family associated RCC | TFE3, TFEB | IHC, FISH, sequencing |
| SDH deficient RCC | SDHB, SDHA, SDHC, SDHD | IHC, sequencing |
| FH deficient RCC | FH, 2SC | IHC, sequencing |
| Angiomyolipoma | TSC1, TSC2 | Sequencing |
| Renal Adenomyomatous Tumor | TCEB1, TSC1, TSC2, mTOR | Sequencing |
| Renal Medullary Carcinoma<br>RCC unclassified with medullary phenotype | SMARCB1 | IHC, FISH, sequencing |
| ALK rearranged RCC | ALK | IHC, FISH, sequencing |
| Hemangioblastoma | VHL | Sequencing, methylation assays |

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**TABLE 1.** Hereditary RCC Syndromes

| Syndromes | Gene | Histologic Types of Renal Tumors | Incidence of Renal Cancer and Mean Age at Diagnosis |
|---|---|---|---|
| VHL disease | *VHL* 3p25-26 | Clear cell RCC | 25%-45%<br>40 y |
| Hereditary papillary RCC | *MET* 7q31 | Papillary RCC type 1 | Unknown<br>< 60 y |
| BHD syndrome | *BHD* 17p11.2 | Hybrid oncocytic/chromophobe RCC<br>Oncocytoma<br>Clear cell RCC<br>Papillary RCC | 34%<br>50 y |
| HLRCC | *FH* 1q42-43 | Heterogenous, but predominantly papillary RCC type 2-like | 2%-21%<br>46 y |
| TSC | *TSC1*/*TSC2* 9q34/16p13 | AML<br>Renal cysts<br>Papillary RCC<br>Clear cell RCC<br>Oncocytoma | 2%-4%<br>30 y |
| Hereditary paraganglioma-pheochromocytoma syndrome | *SDHB*/*SDHC*/*SDHD* 1p36/1q21/11q23 | Clear cell RCC | 5%-15%<br>30 y |
| Hereditary sickle cell hemoglobinopathy and medullary RCC | | Medullary RCC | 10-30 y |
| Germline PTEN mutation Cowden syndrome | *PTEN* 10q22-23 | Clear cell RCC<br>Papillary RCC<br>Chromophobe RCC | 34%<br>40 y |
| Hyperparathyroidism-jaw tumor syndrome | *HRPT2* 1q21-32 | Mixed epithelial and stromal tumor<br>Papillary RCC<br>Wilms tumor | — |
| BAP1 mutations and familial kidney cancer | *BAP1* 3p21 | Clear cell RCC | — |
| Constitutional chromosome 3 translocation RCC | Unknown chromosome 3 | Clear cell RCC | Unknown |

Adeniran et al. Am J Surg Pathol 2015;39:e1–e18

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**CRITERIA FOR FURTHER GENETIC RISK EVALUATION FOR HEREDITARY RCC SYNDROMES[a]**

- **An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene**
- **An individual with RCC with any of the following criteria:**
  - **Diagnosed at age ≤46 y**
  - **Bilateral or multifocal tumors**
  - **≥1 first- or second-degree relative[b] with RCC**
- **An individual whose tumors have the following histologic characteristics:**
  - **Multifocal papillary histology**
  - **Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC, RCC with fumarate hydratase (FH) deficiency or other histologic features associated with HLRCC**
  - **Birt-Hogg-Dubé syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)**
  - **Angiomyolipomas of the kidney and one additional tuberous sclerosis complex criterion in the same person (See Table 1)**
  - **Succinate dehydrogenase (SDH)-deficient RCC histology[c]**

NCCN Guidelines Kidney Version 4.2022

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## Case 2

- 31 y M
- Diagnosed with renal cell carcinoma
- Nephrectomy in Turkey
- Widespread metastatic disease
- Compressive disease L2- nerve root decompression

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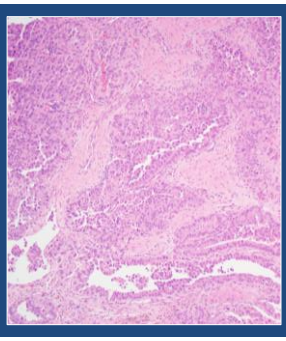
## Case 2



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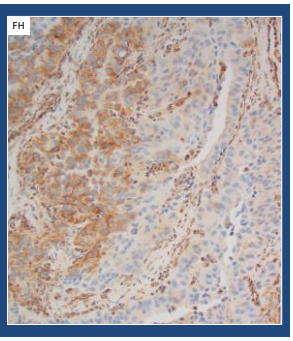
## Case 2: Pathology

- Consistent with metastatic RCC
- Additional testing
  - *TFE3* FISH: negative
  - FH stain: loss of FH in 40% tumor
- Heterogeneous loss: compatible with FH deficient RCC




Anderson WJ et al. Int J Surg Pathol. 2022 Online ahead of print

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## Case 2

- Genetic testing: *FH* c.697C>T p.R233C mutation, heterozygous
- Treatment with Bevacizumab/Erlotinib based on data presented at ASCP 2020
- Tolerated well, interim decrease in metastatic disease
- Hospice
- Disease recurrence
- DOD 1 year later

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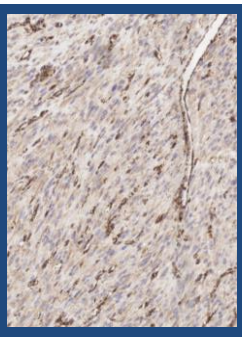
## FH staining interpretation

- Sensitivity: 80-90%
- 2SC IHC stain: greater sensitivity, not widely available



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## Case 3

- 36 y M with renal mass
- Nephrectomy performed at outside hospital
- Family history-
  - Maternal grandfather- testicular cancer

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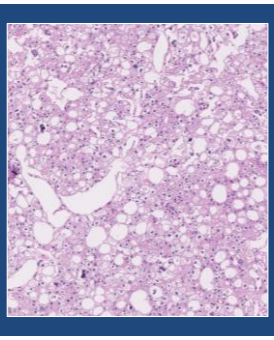

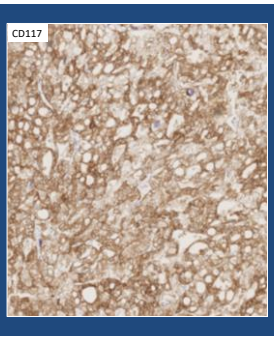


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## Case 3

- Additional history:
  - Spontaneous pneumothorax in childhood
  - Skin lesions
- Genetic testing done because of age and associated clinical stigmata
- Likely pathogenic mutation: *FH* c.1431_1433dup p.Lys477dup
- Request to re-evaluate pathology for FH deficient RCC

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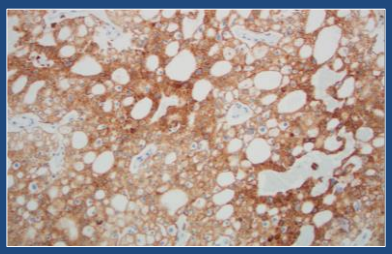
## FH IHC



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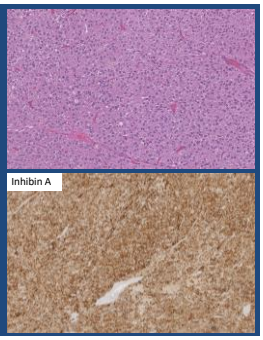
## *FH* alterations also seen in

- Leydig cell tumor

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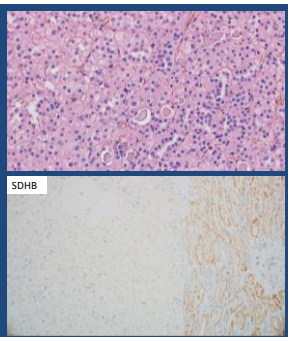
## SDHB

- SDH complex- mitochondrial complex II
  - Four subunits (SDHA, B, C, and D)
- Pheochromocytoma/paraganglioma
- GIST
- Rarely RCC
- SDHB- 80%
- SDHB IHC: screening
  - May not detect SDHA deficient cases
  - SDHD- may show weak staining

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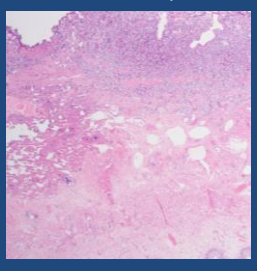
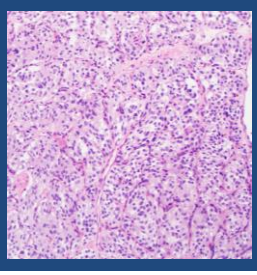
## SDH deficiency also seen in….. Paragangliomas





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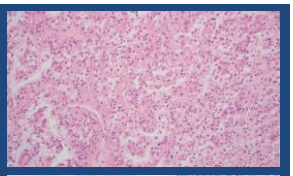
## MiT Family Translocation RCC

- *TFE3, TFEB, TFEC*, and *MiTF*
- Xp11.2 translocation RCC
  - *TFE3* gene on chromosome Xp11.2
  - Partner genes: *PRCC, ASPL*, others
  - Over-expression of the *TFE3* protein
  - Chimeric *TFE3* fusion protein bind to *MET* promoter

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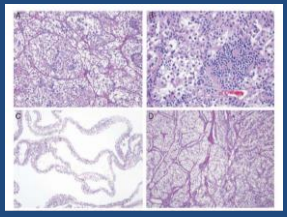
## MiT Family Translocation RCC

- t(6;11)(p21;q12): *Alpha-TFEB* fusion
  - Over-expression of TFEB transcriptional factor gene
  - TFEB- FISH
- Rare cases with *TFEB* amplification also reported



Smith NE et al. Am J Surg Pathol. 2014; 38(5): 604–614
Argani P et al. Am J Surg Pathol. 2016; 40(11): 1484-1495

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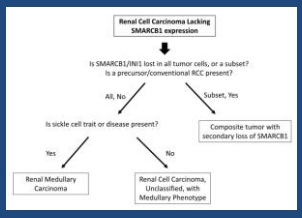
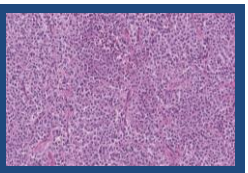
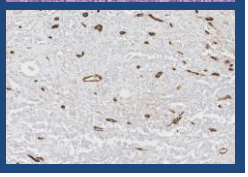
## SMARCB1





Sirohi D et al. Seminars in Diagnostic Pathology 38(2021):212-221

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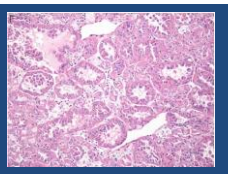
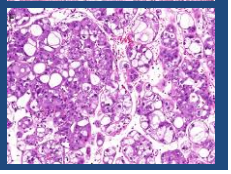
## RCCs with *TSC/MTOR* mutations

- Renal adenomyomatous tumor
- Eosinophilic solid and cystic RCC
- Eosinophilic and vacuolated tumor





Trpkov et al. Am J Surg Pathol 2017;41:1299–1308
Chen Y et al. Am J Surg Pathol. 2019 January ; 43(1): 121–131

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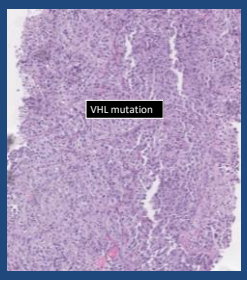
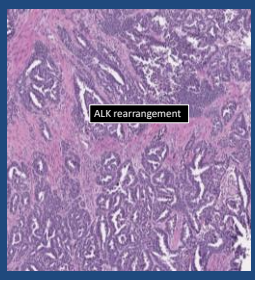
## Unclassified RCC

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| Histopathology | Diagnostic marker | Diagnosis | Significance |
|---|---|---|---|
| Unclassified | VHL p.C77* | ccRCC | Diagnostic, germline HNF1A-risk factor |
| Favor Sarcomatoid Chromophobe | TP53 p.M237K with LOH | Chromophobe | Diagnostic |
| Poorly differentiated | TERT promoter, VHL p.I151T | ccRCC | Diagnostic |
| CDC Vs Urothelial Vs RCC | NF2 p.E530fs- hemizygous | pRCC | Diagnostic |
| Possible distal nephron origin | BRD4-NUTM1 fusion | NUT midline carcinoma | Diagnostic, therapeutic |
| Metastatic carcinoma- favor renal primary | FH c.267+1G>T, hemizygous | FH deficient RCC | Diagnostic, germline ATM |
| Unclassified | None | Unclassified | Unclassified |
| Type II pRCC | TFE3-PRCC fusion | TFE3-RCC | Diagnostic |
| Unclassified | Somatic- TSC2 c.3132-2A>G Germline TSC2 p.A614D | TSC-RCC | Diagnostic |
| Unclassified | TFE3-PRCC fusion | TFE3-RCC | Diagnostic |

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## Aggressive Unclassified RCCs

| 55% | 45% |
| --- | --- |
| • NF2 loss and dysregulated Hippo–YAP signaling (18%)<br>  • Worse outcomes<br>• Hyperactive mTORC1 signaling (26%)<br>  • Better outcomes, therapeutic target<br>  • MTOR, TSC1, TSC2, PTEN<br>• FH: worse outcomes<br>• ALK | • Chromatin modulation (13%)<br>  • Intermediate outcomes<br>  • (SETD2, BAP1, KMT2A/C/D, PBRM1)<br>• DNA damage response (8%)<br>  • (TP53, CHEK2, BRCA2)<br>• No recurrent molecular features (24%) |

Chen Y-B et al. Nat Commun. 2016;7:13131

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## Bladder and Prostate

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## Case 4

- 64 y M
- History of prostate carcinoma, status post radiation
- Bladder mass
- Transurethral resection

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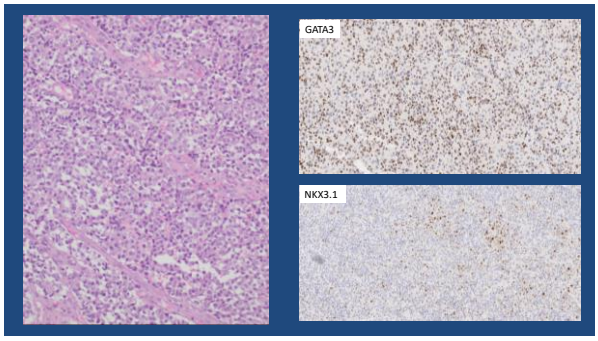


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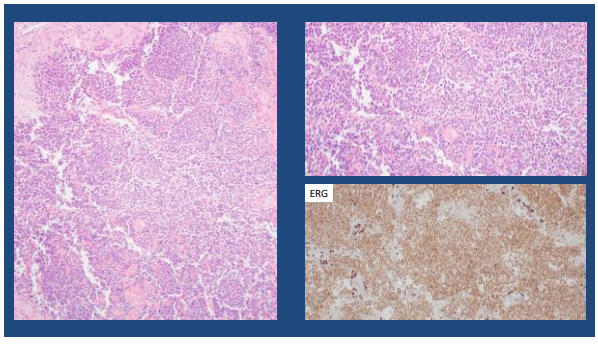


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## Case 4

- Genetic testing: *TMPRSS2-ERG* rearrangement
- Diagnostic of prostate carcinoma

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## ERG

- *ERG* rearrangements in ~50% of prostate carcinoma
- Also seen in high grade prostatic intraepithelial neoplasia
- In Castration resistant prostate carcinoma (CRPC)- protein expression may be reduced/absent
- Testing methods: IHC, FISH, sequencing

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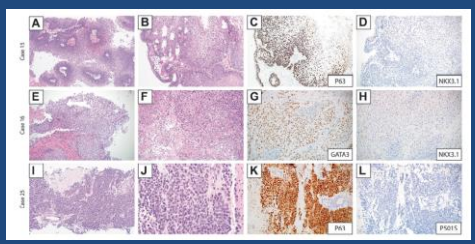
## IHC and Molecular Discordances




Chen E at al. Mod Pathol 2020;33(9):1802-1810

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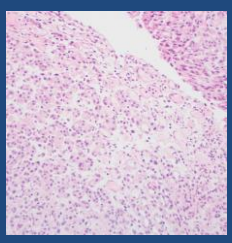
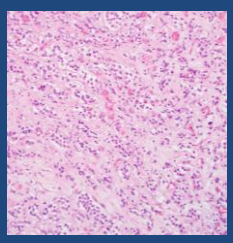
## Bladder: Reactive Vs Neoplastic



Nephrogenic Adenoma



Urothelial carcinoma, nested variant

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## Bladder: Reactive Vs Neoplastic

- *TERT* promoter mutations
  - 60-80% of urothelial carcinomas
  - Early event
  - Seen in both benign and malignant urothelial neoplasms
- Rare in prostate carcinoma
- Utility
  - Reactive vs neoplastic
  - Urothelial carcinoma vs prostate carcinoma
  - Urine screening for disease recurrence

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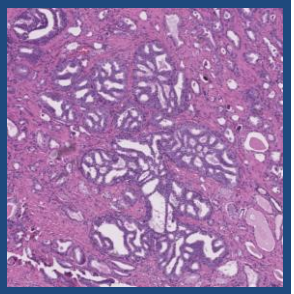
## Case 5

- 65 y M
- 5/2021: Presented with 9 months history of progressive left hip pain
  - Imaging: 6 cm prostate, destructive femoral lesion
  - Left femur biopsy



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## Case 5

- Treatment: Bicalutamide
- 8/2021: Pulmonary nodules
  - Tumor genetic testing: *BRCA2* copy number loss
- 10/2021: clinical trial for DDR mutated gene
- 12/2021: improving pelvic adenopathy

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## Somatic Tumor Testing: NCCN Recommendations

- Purpose
  - Treatment decisions
  - Genetic counseling
  - Clinical trial eligibility
- Testing recommendations
  - Metastatic/regional cancer
    - HRD genes: *BRCA1, BRCA2, ATM, PALB2,FANCA, RAD51D, CHEK2, CDK12*
  - Metastatic CRPC, castration naïve metastatic/regional cancer
    - Microsatellite instability
  - Metastatic CRPC
    - Tumor mutational burden

NCCN Guidelines Prostate Version 3.2022

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## Germline testing: NCCN Recommendations

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

**Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:**

- By Prostate Cancer Stage or Risk Group (diagnosed at any age)
  - Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer
- By Family History[6] and/or Ancestry
  - ≥1 first-, second-, or third-degree relative with:
    - breast cancer at age ≤50 y
    - colorectal or endometrial cancer at age ≤50 y
    - male breast cancer at any age
    - ovarian cancer at any age
    - exocrine pancreatic cancer at any age
    - metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  - ≥1 first-degree relative (father or brother) with:
    - prostate cancer[1] at age ≤60 y
  - ≥2 first-, second-, or third-degree relatives with:
    - breast cancer at any age
    - prostate cancer[1] at any age
  - ≥3 first- or second-degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM*
  - Ashkenazi Jewish ancestry
- Personal history of breast cancer

**Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:**

- By Prostate Cancer Tumor Characteristics (diagnosed at any age)
  - intermediate-risk prostate cancer with intraductal/cribriform histology[7]
- By prostate cancer[2] AND a prior personal history of any of the following cancers:
  - exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

NCCN Guidelines Prostate Version 3.2022

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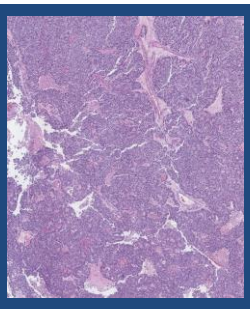

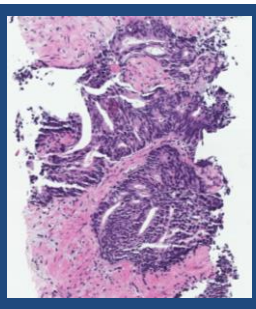

BRCA alterations: more frequent in ductal and cribriform histology

Velho PI et al. Prostate. 2018;78(5):401-407

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# Testicular Tumors

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## Case 6

- 39 y M
- 2/2019:
  - Abdominal pain while on a vacation
  - CT scan at ED: 12 cm retroperitoneal mass
  - Testicular exam: negative
  - Elevated AFP
  - Biopsy: Yolk Sac Tumor
  - Bleomycin, etoposide, cisplatinum
- 6/2019: residual disease
  - Retroperitoneal mass excision

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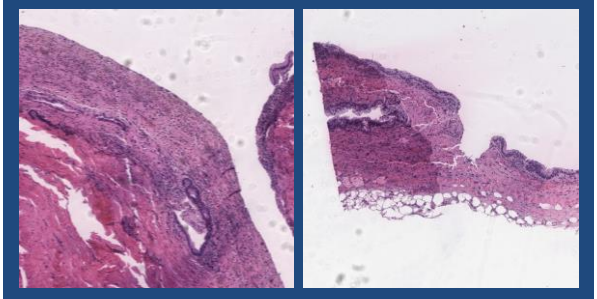

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## Case 6

- SALL4: focally positive
- Cyst with enteric lining compatible with residual teratoma
- Isochromosome 12p (FISH): Positive

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## Isochromosome 12p

- Present in ~80% of germ cell tumors
- Testing methods: FISH, sequencing, genomic array
- Utility
  - Prepubertal vs postpubertal teratoma
  - Characterizing somatic type malignancy as of germ cell origin
- Also seen in ovarian and extragonadal germ cell tumors

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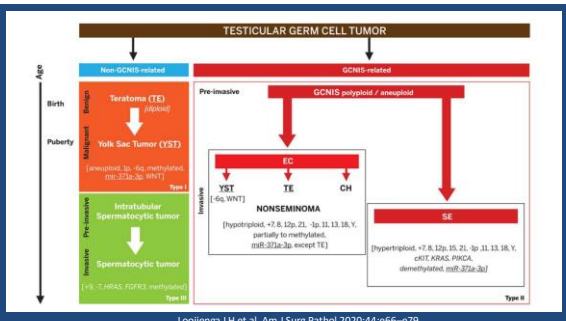


Looijenga LH et al. Am J Surg Pathol 2020;44:e66–e79

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# Penile Carcinomas

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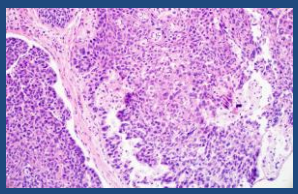
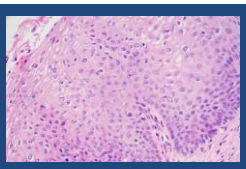
## HPV Related Changes



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## HPV driven Penile carcinomas

- ~ 50%
- HPV driven- better prognosis
- Testing methods:
  - H&E morphology
  - p16 IHC
  - HPV ISH
  - PCR

**TABLE 2.** WHO Classification of PeIN

| |
|---|
| Non–HPV-related |
| Differentiated |
| HPV-related |
| Basaloid |
| Warty |
| Warty-basaloid |
| Other |
| Pleomorphic |
| Spindle |
| Clear cell |
| Pagetoid |

Canete-Portillo S et al. Am J Surg Pathol 2020;44:e80–e86

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# Immunotherapy Biomarkers

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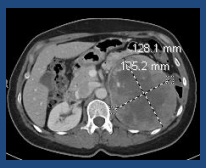
## Case 7

- 52 y F
- 2017: Pelvic mass- incidentally discovered on abdominal imaging adjacent to upper pole of left kidney
- Family history of cancer: mother, paternal grandfather
- Biopsy, adrenalectomy

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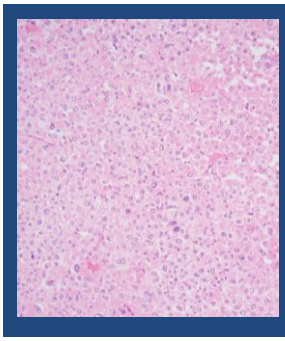

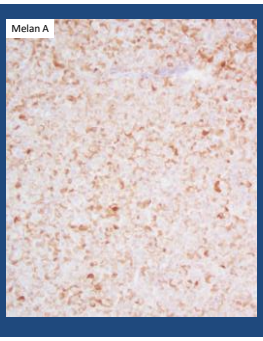


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## Case 7

- Diagnosis: Adrenal cortical Carcinoma
- 5/2019: Lucent bone lesions vertebral bodies, lung lesions. Bone biopsy- c/w metastatic adrenal cortical carcinoma
- 7/2019: Nivolumab/Ipilumab
- 12/2021: unchanged bone lesions
  - Likely treated disease on bone scans
  - Lung lesions- resolved, no new lesions
  - Ongoing response
- *PMS2* mutation: c.736_741delCCCCCTins11
- Hereditary non-polyposis colorectal cancer/Lynch syndrome

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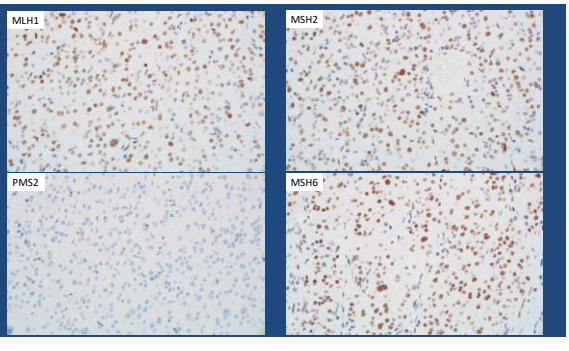


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## Microsatellite instability/Mismatch Repair Protein Deficiency

- MSI/MMR: eligibility for immunotherapy
- Agnostic of tumor type
- Testing methods:
  - MMR IHC: MLH1/PMS2, MSH2/MSH6
  - Next generation sequencing
  - MSI PCR

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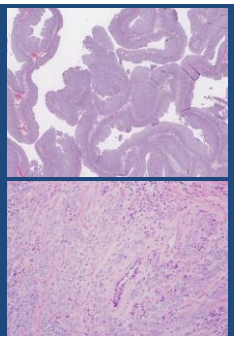
## Genitourinary tumor in HNPCC syndrome

- Upper urothelial tract carcinoma ~ 1-5%
- Prostate carcinoma ~ 2%
- Adrenal cortical carcinoma



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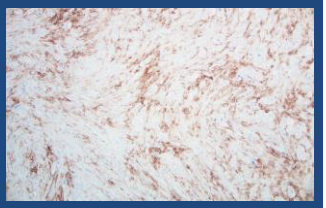
## PD-L1 and Tumor Mutational Burden

- PD-L1:
  - Urothelial carcinoma
    - PD-L1 28-8: Nivolumab
    - SP-142: Atezolizumab
- Tumor Mutational Burden
  - Lacks standardization
  - High TMB- targetable



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Thank you

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