KIDNEY CANCER

Kidney Cancer: Documentation for AI & RAG Functionality

I. Normal Kidney Tissue (Healthy Kidney Tissues)

This section establishes the morphological and immunohistochemical baseline for non-malignant tissue, essential for differential diagnosis.

Category	Key Technical Data	Relevance for AI (Input/Output)
Gross Anatomy	Capsule intact, smooth contour, typically reddish-brown cortex. Clear demarcation between cortex (containing glomeruli and convoluted tubules) and medulla (containing loops of Henle and collecting ducts).	**Input:** Imaging baseline (CT/MRI) for mass effect, contour, and vascularity.
Normal Histology	**Glomeruli** with distinct capillary loops; **Proximal and Distal Tubules** lined by cuboidal cells with uniform, round, basal nuclei. Distinct brush borders on proximal tubules.	**Input:** Recognition of **uniform nuclear size/polarity** and organized architecture.
Cytology	Cells are small, with uniform nuclei and minimal cytoplasm, maintaining a low nuclear-to-cytoplasmic ratio. Absence of pleomorphism, hyperchromasia, and atypical mitotic figures.	**Output RAG:**Confirmation of absence of malignancy and nuclear grade 1 features.
Immunomarkers	Tubules: Positive for **PAX8, PAX2, CD10, Vimentin** (variable). Glomeruli: **WT1** (Podocytes).	**Baseline Immunophenotyping** to confirm renal origin.
Function (Lab)	Normal Glomerular Filtration Rate (GFR), Blood Urea Nitrogen (BUN), and Creatinine levels.	**Input:** Clinical correlation (Renal function preservation).

II. Tumor (Tumor-Affected Kidney Tissues)

This section focuses on the two most common malignant renal tumors: **Renal Cell Carcinoma (RCC)**, emphasizing the main subtypes (Clear Cell, Papillary, Chromophobe), and **Urothelial Carcinoma** of the renal pelvis.

A. Renal Cell Carcinoma (RCC) - The Main Malignancy

Category	Key Technical Data	Relevance for AI (Input/Output)
Gross Anatomy (RCC)	Typically solid, well-circumscribed, often with **hemorrhage, necrosis, and cystic change**. Clear Cell RCC is often golden-yellow. Papillary RCC is typically tan/brown.	**Input:** Imaging features (Enhancement pattern, fat content, calcification).
Staging (TNM)	**T (Tumor):** Based on size and local invasion (e.g., T1 cm, T4 invasion beyond Gerota's fascia). **N (Node):** Regional lymph node metastasis. **M (Metastasis):** Distant spread (lung, bone, liver, brain).	**Input:** TNM stage (Crucial for prognosis and treatment selection).
Prognostic Grading	**Fuhrman/ISUP Grading:** Based on **Nuclear Size, Shape, and Nucleolar Prominence**. Graded 1 (minimal deviation) to 4 (highly anaplastic/sarcomatoid).	**Input:** ISUP Grade (Strongest predictor of overall survival for localized disease).
ICD-O Code	8310/3 (Renal Cell Carcinoma, NOS).	**Output:** Coding and reporting.

B. Major RCC Subtypes and Molecular Profiles

Subtype	Histological Features	Molecular/Genetic Alteration	Therapeutic/Prognostic Implication for AI/RAG
Clear Cell RCC (ccRCC)	**Clear cytoplasm** (due to lipid/glycogen), nested/alveolar pattern, delicate vasculature.	**VHL Gene Inactivation**(mutation or hypermethylation) in of cases. Results in activation of HIF pathway.	**Prognosis:** Intermediate. **Treatment Focus:** Targeting **VEGF pathway**(Bevacizumab, Pazopanib) and **mTOR pathway** (Everolimus).
Papillary RCC (pRCC)	Tumors composed of **papillae**(finger-like projections) lined by cuboidal cells; often classified as Type 1 (basophilic, low grade) or Type 2 (eosinophilic, high grade).	**Type 1:** Trisomy of Chromosomes **7** and **17**. **Type 2:** More complex karyotypes, often more aggressive.	**Prognosis:** Generally better than ccRCC, especially Type 1. **Treatment:** Similar to ccRCC (VEGF/mTOR), but often less responsive.
Chromophobe RCC (chRCC)	Cells with **prominent cell borders**and abundant pale/eosinophilic cytoplasm;	**Multiple Chromosome Losses** (Hypodiploidy).	**Prognosis:** Best prognosis among the major subtypes. **Treatment:**Less aggressive systemic therapy typically needed; often resistant to standard targeted agents.

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	often perivascular clearing (like plant cells).		

C. Urothelial Carcinoma of the Renal Pelvis

Category	Key Technical Data	Relevance for AI (Input/Output)
Definition	Malignancy arising from the transitional epithelium lining the renal pelvis (analogous to bladder cancer).	**Differential Diagnosis:** Crucial to distinguish from RCC (different primary treatment).
Histology	Cells resembling normal urothelium but with architectural and nuclear atypia. Often multifocal (pelvis, ureter, bladder).	**Input:** Recognition of **non-renal**(urothelial) differentiation.
Immunomarkers	Positive for **CK7, GATA3, and Uroplakin**. Negative for typical RCC markers (PAX8, CD10).	**RAG Output:** Confirms urothelial origin for treatment planning.
Treatment Modality	**Nephroureterectomy** (entire kidney and ureter removed) due to high risk of spread along the urinary tract.	**Output:** Requirement for radical surgery extending beyond simple nephrectomy.

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Normal Histology	**Glomeruli** with distinct capillary loops; **Proximal and Distal Tubules** lined	**Input:** Recognition of **uniform nuclear**

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	by cuboidal cells with uniform, round, basal nuclei. Distinct brush borders on proximal tubules.	**size/polarity** and organized architecture.
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Esporta in Fogli

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Treatment Modality	**Nephroureterectomy** (entire kidney and ureter removed) due to high risk of spread along the urinary tract.	**Output:** Requirement for radical surgery extending beyond simple nephrectomy.

Kidney Cancer (Renal Cell Carcinoma) and Normal Kidney Tissue

(Optimized for Clinical Practice and AI/RAG Applications – November 2025)

This document focuses on the two primary categories used in public AI pathology datasets (e.g., TCIA kidney datasets, Kaggle renal cell carcinoma histopathology images):

1. Normal kidney tissue
2. Tumor (predominantly renal cell carcinoma, RCC)

1. Normal Kidney Tissue

Macroscopic

- Cortex: tan-brown, granular
- Medulla: pale pyramids
- Clear demarcation cortex/medulla, no masses

Microscopic Landmarks (key for AI training)

Structure	Histology Features	Staining Characteristics
Glomeruli	20–50 capillary tufts, Bowman capsule, mesangial cells	PAS+ basement membranes
Proximal tubules	Cuboidal cells, eosinophilic cytoplasm, brush border	PAS+ brush border
Distal tubules / collecting ducts	Clearer cytoplasm, distinct cell borders	Less eosinophilic
Loops of Henle	Thin squamous epithelium	—
Interstitium	Sparse fibroblasts, vasa recta	—
Vessels	Thick-walled arteries, thin veins	Elastic stain helpful

Immunohistochemistry (normal expression)

- PAX8 + (nuclear, all tubular cells and glomeruli)
- CD10 + (proximal tubules)
- RCC antigen + (proximal tubules)
- AMACR (P504S) + (proximal tubules)
- CK7 variable (distal > proximal)

2. Tumor (Renal Cell Carcinoma – RCC)

Epidemiology (2025) ~81,000 new cases/year USA; M:F 2:1; peak 60–70 y. Risk factors: smoking, obesity, hypertension, acquired cystic disease, hereditary syndromes (VHL, BHD, HLRCC, tuberous sclerosis).

WHO/ISUP 2022 Classification (most common subtypes in datasets)

Subtype	Frequency	Key Genetics/Molecular	Histopathology (H&E)	WHO/ISUP Grade	Prognosis	IHC Profile
Clear cell RCC (ccRCC)	70–80%	VHL inact (90%), 3p loss, PBRM1, SETD2, BAP1	Clear cells (lipid/glycogen), delicate vessels, nested/alveolar	1–4 (Fuhrman replaced by nucleolar prominence + extreme pleomorphism)	Worst among common	CAIX + (box-like), CD10 +, PAX8 +, vimentin +
Papillary RCC (Type 1)	10–15%	MET alterations	Papillae with fibrovascular cores, foamy macrophages, cuboidal cells	1–3	Intermediate	AMACR +, CK7 +, RAC2 +
Papillary RCC (Type 2)	5–10%	FH mutation (HLRCC), CDKN2A	Higher grade, eosinophilic cytoplasm	3–4	Poor	AMACR +, CK7 variable
Chromophobe RCC (classic)	5%	Multiple chr loss, TERTp	Pale/eosinophilic cells, raisinoid nuclei, perinuclear halos	Not graded (better prog)	Best	CK7 diffuse +, CD117 +, PAX8 +
Chromophobe hybrid / oncocytic	Rare	Birt-Hogg-Dubé (FLCN)	Oncocytic, variable	—	Variable	Same as chRCC
Clear cell papillary renal cell tumor (2022: no longer RCC)	2–4%	Benign/indolent	Clear cells, low-grade nuclei aligned at apical	—	Excellent	CAIX cup-like +, CK7 diffuse +, CD10 –
Oncocytoma (benign)	5–10%	chr1 loss, mtDNA mutations	Nested oncocytic cells, no clear cells	—	Benign	CK7 patchy/focal, CD117 +

Emerging Entities (2025)

- Eosinophilic solid & cystic RCC (TSC/MTOR mutations)
- FH-deficient RCC (very aggressive)
- ALK-rearranged RCC (children/young adults)
- SMARCB1-deficient renal medullary carcinoma (poor prog, sickle-cell trait)

Grading (WHO/ISUP 2022)

- Grade 1: inconspicuous nucleoli at 100×
- Grade 2: prominent nucleoli at 100×
- Grade 3: prominent at 40×
- Grade 4: extreme pleomorphism, rhabdoid/sarcomatoid, tumor giant cells
  Sarcomatoid/rhabdoid dedifferentiation (any subtype) → pT3 at minimum, very poor prognosis.

Staging (AJCC 8th ed. 2017 + 2025 updates)

- pT3a: fat invasion (perinephric/sinus) or renal vein
- pT3b/c: vena cava
- Grade, necrosis, sarcomatoid now incorporated into prognostic models.

Prognostic Scoring (2025)

Score	Factors	Use
MSKCC/IMDC (metastatic)	KPS, time from dx, Hb, Ca, LDH, neutrophils	Targeted therapy/IO era still valid
UCLA Integrated Staging System (localized)	Stage + grade + necrosis + performance status	Postoperative nomograms
Leibovich (post-nephrectomy)	Stage, size, grade, necrosis, microvascular invasion	Clear cell only

Key Immunohistochemistry Panel (for AI and differential diagnosis)

Marker	Normal Kidney	Clear Cell RCC	Papillary RCC	Chromophobe RCC	Oncocytoma	Collecting Duct / Medullary
PAX8	+	+	+	+	+	+
CAIX	–	+ (membranous box)	–	–	–	–
CD10	+ (proximal)	+	+ (Type 1)	–	–	Variable
CK7	+ (distal)	–/focal	+ diffuse	+ diffuse	–/patchy	+
AMACR	+ (proximal)	–/weak	+	–	–	+

Marker	Normal Kidney	Clear Cell RCC	Papillary RCC	Chromophobe RCC	Oncocytoma	Collecting Duct / Medullary
CD117 (c-KIT)	–	–	–	+	+	–
Vimentin	–	+	+	–	–	+
GATA3	–	–	–	–	–	+ (medullary)

Management Summary (NCCN/EAU 2025)

Stage	First-Line (Localized)	Metastatic/Advanced (Clear Cell)
Stage I–II	Partial nephrectomy preferred (if feasible) → observation	—
Stage III	Radical nephrectomy + lymph node dissection if indicated	—
Stage IV / Recurrent	Cytoreductive nephrectomy in selected patients + systemic	IO-based: pembro + axitinib, nivo + cabozantinib, pembro + lenvatinib (Category 1) HIF-2α inhibitor: Belzutifan (VHL disease or sporadic ccRCC post-IO/TKI)
Non-clear cell	Clinical trial or sunitinib/ cabozantinib	Cabozantinib or IO/TKI combinations

Key Take-Home for Pathologists/AI Applications

- In most public datasets, “Tumor” = clear cell RCC (70–80% of images)
- Normal kidney shows preserved architecture, no nuclear atypia, clear cortex/medulla distinction
- Critical AI features for malignancy: clear cytoplasm (ccRCC), papillary structures (papillary), plant-like cells + halos (chromophobe), oncocytic nests (oncocytoma/benign)
- Always combine morphology with IHC (PAX8/CAIX/CD10/CK7) for accurate subtyping

Kidney Cancer (Renal Cell Carcinoma) – Imaging and Biopsy Details

(Updated November 2025 – EAU, AUA, NCCN, ESR guidelines)

Multimodality Imaging of Renal Masses (2025)

Modality	Key Indications	Typical Findings – Benign/Normal Kidney	Typical Findings – RCC (Tumor)	Bosniak 2019/2024 Class (Cystic)	Comments
Ultrasound (US)	Initial detection of incidental mass, cystic vs solid differentiation	Normal parenchyma echogenicity, clear cortex/medulla	Solid hypoechoic/isoechoic mass with vascularity on Doppler; cystic with thick septa/wall/nodules	—	First-line, no radiation; limited for staging
Contrast-enhanced CT (CECT)	Gold standard for characterization and staging of solid/cystic masses	Homogeneous enhancement of normal parenchyma	>20 HU enhancement in corticomedullary phase; heterogeneous, necrotic areas (clear cell), washout	Bosniak III–IV → surgical	4-phase protocol: non-con, corticomedullary, nephrographic, excretory
MRI (with gadolinium)	Problem-solving (young patients, allergy to iodine, indeterminate cysts, venous involvement)	Normal T1/T2 signal, homogeneous enhancement	Clear cell: T2 hyperintense, avid enhancement, microscopic fat rare; papillary: T2 hypointense, mild enhancement	Same as CT	Superior soft-tissue contrast; chemical shift for microscopic fat (ccRCC)
CEUS (contrast-enhanced US)	Alternative when CT/MRI contraindicated	Homogeneous parenchymal blush	Hyperenhancement in clear cell, hypoenhancement in papillary/chromophobe	Emerging role	No radiation/nephrotoxicity
PET-CT (18F-FDG)	Limited role (generally not recommended for primary); useful in metastatic/restaging	No uptake	Variable (clear cell > papillary); better with 89Zr-girentuximab (CAIX) or 68Ga-PSMA in some trials	—	Not routine

Bosniak Classification v2019/2024 (CT & MRI) – Determines Management

Class	Features	Malignancy Risk	Management (2025)
I	Simple cyst, no septa/wall/nodules	~0%	Ignore
II	Few thin septa, fine calcification	<1%	Ignore
IIF	Multiple thin septa, minimal smooth thickening, perceived enhancement	5–10%	Follow-up 6–12 mo then yearly ×5 y

Class	Features	Malignancy Risk	Management (2025)
III	Thick/irregular walls/septa, measurable enhancement	50–60%	Surgical (partial preferred) or ablation
IV	Soft-tissue enhancing nodules	>90%	Surgical

Key Imaging Features by RCC Subtype (for AI correlation)

Subtype	CT Enhancement Pattern	MRI T1/T2 Signal	Other Clues
Clear cell RCC	Strong heterogeneous enhancement, washout, necrosis	T2 hyperintense, microscopic fat (drop on opposed-phase)	Most vascular
Papillary RCC	Mild, gradual enhancement	T2 hypointense (hemosiderin), no fat	Hypovascular
Chromophobe RCC	Moderate, spoke-wheel enhancement	T2 variable, hypointense rim (occasional)	Central scar rare
Oncocytoma	Variable, often spoke-wheel or stellate scar	Similar to chromophobe	Cannot reliably distinguish from chRCC on imaging

Biopsy Details in Renal Masses (EAU/AUA 2025 Guidelines)

Indication for Biopsy	Technique & Approach	Yield & Accuracy	Complications
Mandatory/Strongly Recommended: - Small cortical neoplasm (<4 cm) candidate for active surveillance or ablation - Suspected lymphoma, metastasis, or abscess - Before systemic therapy in metastatic setting	Percutaneous core biopsy (18G preferred) under US or CT guidance Coaxial technique → 2–4 cores FNA rarely sufficient alone	Diagnostic yield 88–96% Subtype concordance ~90–95% Grade concordance lower (~70%, especially Fuhrman/ISUP 2 vs 3)	Bleeding <5%, clinically significant <1% Tumor seeding <0.01% (modern series) Pneumothorax (if transpleural)
Optional: Solid enhancing mass in patient fit for surgery (many centers still biopsy small masses)	Avoid FNA only (insufficient for architecture)	—	—

Biopsy Results Interpretation

Finding	Clinical Implication
Clear cell RCC, ISUP 1–2	Partial nephrectomy or ablation if small
Clear cell RCC, ISUP 3–4 or sarcomatoid	Higher risk of progression; favors surgery over surveillance
Oncocytoma or other benign	Active surveillance safe

Finding	Clinical Implication
Chromophobe RCC	Excellent prognosis; surveillance possible in small tumors
Non-diagnostic (necrosis/fibrosis)	Repeat biopsy or proceed to surgery/ablation

Immunohistochemistry on Biopsy (essential when material is limited)

Marker	Clear Cell	Papillary	Chromophobe	Oncocytoma
CAIX	+ (box)	–	–	–
CD10	+	+	–	–
CK7	–/focal	+ diffuse	+ diffuse	patchy
AMACR	–	+	–	–
CD117	–	–	+	+

Key 2025 Take-Home Messages for Imaging + Biopsy

1. **CECT or MRI** is mandatory for characterization; US alone is insufficient for solid masses.
2. **Biopsy is now routinely recommended** for small renal masses (<4 cm) before active surveillance, thermal ablation, or in metastatic patients to guide systemic therapy.
3. In most AI datasets, "Tumor" = biopsy-proven RCC (predominantly clear cell); "Normal" = non-neoplastic parenchyma from nephrectomy specimens.
4. Percutaneous core biopsy is safe and accurate for subtype diagnosis; oncocytoma vs chromophobe remains the most common diagnostic challenge even with IHC.

Molecular Diagnostics in Renal Cell Carcinoma (RCC) – 2025 Clinical Guide

Molecular testing has moved from research to **routine clinical practice** in RCC, driven by:

1. Accurate subtyping (especially non-clear cell)
2. Prognostic stratification
3. Selection of targeted therapies (mTOR, MET, HIF-2α) and immunotherapy combinations
4. Enrollment in biomarker-driven trials

Current Guidelines Requiring Molecular Testing (2025)

Organization	Recommendation
NCCN v3.2025	NGS recommended for all advanced/metastatic RCC (clear cell and non-clear cell)
EAU 2025	Molecular testing mandatory in non-clear cell and sarcomatoid/rhabdoid cases; strongly recommended in metastatic ccRCC
ESMO 2024	Tumor NGS (DNA + RNA if possible) at diagnosis of advanced disease
ASCO 2025	Routine genomic profiling in metastatic RCC

Recommended Molecular Platforms (2025)

Platform Type	Genes Covered (Typical)	Advantages	Limitations
DNA-based NGS panels	300–500 genes (TSO500, FoundationOne CDx, MSK-IMPACT, Caris, Tempus xT)	Detects SNV, indel, CNV, TMB, MSI	Misses fusions, limited VAF in low-purity samples
DNA + RNA NGS (Archer, Tempus xT, FoundationOne)	Adds fusion detection (MET, ALK, NTRK, etc.)	Highest yield for actionable fusions	Higher cost
Liquid biopsy (ctDNA)	Guardant360, FoundationOne Liquid, Signatera	Non-invasive, monitors evolution, early relapse detection	Lower sensitivity in low-burden disease

Key Actionable/Reportable Alterations in RCC (2025)

Subtype	Alteration	Frequency	Prognostic Impact	Therapeutic Implication (2025)
Clear cell RCC	VHL mutation/3p loss	85–90%	None (truncal)	Required for belzutifan eligibility (VHL disease or sporadic post-IO/TKI)
	PBRM1	40–50%	Favorable with IO	Predicts benefit from nivolumab-based regimens
	SETD2, BAP1	10–15% each	Poor (BAP1 worse)	BAP1 → consider clinical trials
	MTOR pathway (TSC1/2, PI3KCA)	5–10%	Variable	Everolimus or temsirolimus (modest activity)
	TMB-high (>10 mut/Mb)	<5%	Favorable with IO	May predict IO response
Papillary Type 1	MET alteration (mutation or amp)	20–80% (hereditary > sporadic)	—	Cabozantinib or savolitinib (MET Exon 14) preferred
Papillary Type 2 / FH-deficient	FH mutation	100% hereditary, rare sporadic	Very poor	Bevacizumab + erlotinib (historical); IO + TKI trials; consider PARP inhibitors (preclinical)
Chromophobe	TP53, PTEN, FLCN	Variable	Poor if TP53/PTEN	Limited options; mTOR inhibitors in trials
Collecting duct / Medullary	SMARCB1 (INI1) loss	High in medullary	Very poor	EZH2 inhibitors (tazemetostat) in trials

Subtype	Alteration	Frequency	Prognostic Impact	Therapeutic Implication (2025)
Translocation RCC (MiT family)	TFE3/TFEB fusions	Pediatric/young adults	Variable	VEGF-TKI (sunitinib/cabozantinib); IO poor response
Rare fusions	ALK, ROS1, NTRK	<1%	—	Entrectinib/larotrectinib (NTRK), alectinib (ALK)
Sarcomatoid/rhabdoid dedifferentiation	Any subtype + TP53, ATRX, etc.	5–10% ccRCC	Very poor	Nivolumab + ipilimumab or IO + TKI preferred (high response rates)

HIF-2α Pathway – New Standard (2025)

- Belzutifan (oral HIF-2α inhibitor) FDA-approved 2024/2025 for VHL-associated RCC and sporadic ccRCC after IO + TKI.
- Requires confirmation of VHL alteration (germline or somatic) for VHL disease; for sporadic ccRCC, no biomarker required but response higher with intact VHL pathway.

Prognostic Molecular Signatures (2025)

Signature	Platform	Genes	Outcome Prediction
ClearCode34	NanoString/RNA-seq	34	Distinguishes ccA (good) vs ccB (poor)
BIONIKK 16-gene	RNA (Decipher Kidney)	16	Predicts TKI vs IO benefit
IMDC + molecular	NGS + clinical	—	PBRM1 + favorable risk → best IO response

Practical Testing Algorithm (Advanced/Metastatic RCC – 2025)

1. **At diagnosis of metastatic disease**
   - Archival tumor (primary or met) → comprehensive NGS (DNA + RNA if possible)
   - If insufficient tissue → liquid biopsy (ctDNA)
2. **Non-clear cell or sarcomatoid histology**
   - Mandatory NGS + FH immunohistochemistry (for Type 2 papillary suspicion)
3. **Progression on first-line IO/TKI**
   - Re-biopsy if feasible OR liquid biopsy to detect emergence of resistance (e.g., MET amplification after cabozantinib)
4. **VHL disease suspicion (young age, multifocal, CNS hemangioblastoma, pheo)**
   - Germline VHL testing + tumor NGS

Key Take-Home Messages for Clinicians (November 2025)

- **Every advanced RCC patient should have NGS** – it is now standard of care.
- Clear cell: VHL, PBRM1, BAP1, SETD2, mTOR pathway are most clinically relevant.

- Non-clear cell: MET (papillary), FH (HLRCC), FLCN (Birt-Hogg-Dubé), SMARCB1 (medullary) drive therapy.
- Liquid biopsy is acceptable alternative when tissue unavailable; sensitivity ~80–90% in metastatic setting.
- Sarcomatoid/rhabdoid features → treat as aggressive clear cell (IO + TKI preferred); molecular confirmation of underlying subtype still critical.

Molecular diagnostics has transformed RCC from a "one-size-fits-all" VEGF-TKI disease to a highly personalized model with multiple actionable pathways.

Hereditary Renal Cell Carcinoma (RCC) Syndromes – Comprehensive Clinical Guide (November 2025)

Approximately 5–8% of RCC are hereditary. Early recognition is critical: younger age at onset, multifocal/bilateral tumors, family history, extrarenal manifestations → trigger germline testing.

Syndrome	Gene (Inheritance)	Lifetime RCC Risk	RCC Histology (Typical)	Key Extrarenal Manifestations	Screening Recommendations (2025 NCCN/EAU)	First-Line RCC Therapy Notes
von Hippel-Lindau (VHL) disease	VHL (AD)	40–70%	Clear cell RCC (always), multifocal/bilateral, early onset (<40 y)	CNS/retinal hemangioblastomas, pheochromocytoma/paraganglioma, pancreatic cysts/NET, endolymphatic sac tumors	Abdominal MRI/US yearly from age 16 Brain/spine MRI every 2 y from age 16	Belzutifan (HIF-2α inhibitor) now first-line systemic (FDA 2021, expanded 2024–2025) Active surveillance for tumors <3 cm (partial nephrectomy when >3 cm)
Hereditary Papillary RCC (Type 1)	MET (AD)	~100% penetrance	Papillary Type 1 (multiple, bilateral)	Very few extrarenal (rare duodenal cancer)	Renal US or MRI every 1–2 y from age 20–30	Cabozantinib or savolitinib (MET

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						inhibitors) preferred in metastatic
Hereditary Leiomyomatosis and RCC (HLRCC)	FH (AD)	15–30%	Papillary Type 2 or collecting-duct–like, very aggressive	Cutaneous/uterine leiomyomas (nearly 100% women), uterine leiomyosarcoma	Annual renal MRI from age 8–10 (high penetrance, early onset)	Bevacizumab + erlotinib historical; IO + TKI trials; avoid thermal ablation (explosive growth reported)
Birt-Hogg-Dubé (BHD)	FLCN (AD)	15–35%	Hybrid oncocytic/chromophobe (HOCT), chromophobe, oncocytoma	Lung cysts → spontaneous pneumothorax (25–40%), fibrofolliculomas, trichodiscomas	Renal MRI every 3 y from age 20	mTOR inhibitors (everolimus) modest activity; surgery preferred
Tuberous Sclerosis Complex (TSC)	TSC1 or TSC2 (AD)	2–5%	Angiomyolipoma >> RCC; RCC usually oncocytic or chromophobe	Cortical tubers, subependymal nodules, renal AML (70–90%), cardiac rhabdomyomas, skin angiofibromas	Renal MRI every 1–3 y from childhood	Everolimus (mTOR inhibitor) approved for AML and TSC-related tumors

Syndrome	Gene (Inheritance)	Lifetime RCC Risk	RCC Histology (Typical)	Key Extrarenal Manifestations	Screening Recommendations (2025 NCCN/EAU)	First-Line RCC Therapy Notes
Succinate Dehydrogenase (SDH)-deficient RCC	SDHB, SDHC, SDHD (AD)	10–15% (in SDHB)	Oncocytic, SDH-deficient (rare)	Paraganglioma/pheochromocytoma (50–80%), GIST, pituitary adenoma	Annual renal MRI + plasma/urine metanephrines from age 10	Limited data; VEGF-TKI or IO; high PD-L1 expression in some
PTEN Hamartoma Tumor Syndrome (Cowden)	PTEN (AD)	~30–35%	Papillary or chromophobe	Breast, thyroid, endometrial cancer; macrocephaly, trichilemmomas	Renal US/MRI every 3–5 y from age 40	mTOR inhibitors (everolimus) used in some cases
Constitutional chromosome 3 translocation	Various on 3p (AD)	High	Clear cell RCC, bilateral/multifocal	None specific	Annual renal imaging from childhood	Same as sporadic ccRCC
Polymerase Proofreading-Associated Polyposis (PPAP) / CMRD	POLE/POLD1 (AD)	Increased	Variable (often early-onset)	Colorectal adenomas/cancer, brain tumors	Renal imaging every 3–5 y from age 25–30	IO-based regimens (high TMB/MSI-H possible)

Germline Testing Recommendations (NCCN 2025)

Test if ANY of the following:

- RCC diagnosed ≤46 years
- Multifocal or bilateral RCC
- ≥1 first-degree relative with RCC
- Histology suggestive (FH-deficient, SDH-deficient, hybrid oncocytic)
- Personal/family history of syndrome-specific features (e.g., pneumothorax + fibrofolliculomas → BHD)
- ≥10 lifetime renal tumors (VHL suspicion)

Preferred panel: Multigene NGS panel including at least VHL, MET, FH, FLCN, TSC1/2, SDHB/C/D, PTEN, BAP1

Key Clinical Pearls (2025)

1. VHL is the most common and most important hereditary RCC syndrome → belzutifan has revolutionized systemic management.
2. HLRCC (FH) tumors are uniquely aggressive → single metastatic node can kill; early nephrectomy (even for small tumors) often recommended.
3. BHD lung cysts + skin fibrofolliculomas + chromophobe/hybrid tumors = classic triad.
4. Always perform IHC for FH and SDHB on unusual/aggressive non-clear cell tumors → loss triggers germline testing.
5. Active surveillance with serial imaging is standard for VHL, BHD, TSC (tumors grow slowly); threshold for intervention usually 3 cm.

Early recognition of hereditary syndromes dramatically changes surgical timing, systemic therapy choices (belzutifan for VHL, MET inhibitors for hereditary papillary), and family screening.