Hereditary Genitourinary Cancers: When To Be Suspicious and Why

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Objectives

- Describe the red flags of hereditary GU cancer and indications for germline genetic testing
- Review hereditary GU cancer genes
- Explore the cancers associated with hereditary GU cancer genes

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Obtaining a Family History

- Same or related cancers in several relatives
- Younger than average ages of onset
- More than one generation with cancer
- Presence of rare cancers
- Bilateral cancers
- Multiple primary cancers

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Could it be Hereditary?

- General Population Risk of Prostate Cancer: ~12-13%
  - More than 60% of cases are diagnosed after age 65
- ~5-10% of Prostate Cancer is Hereditary
  - Associated with more aggressive disease, including higher likelihood of nodal involvement and distant metastasis

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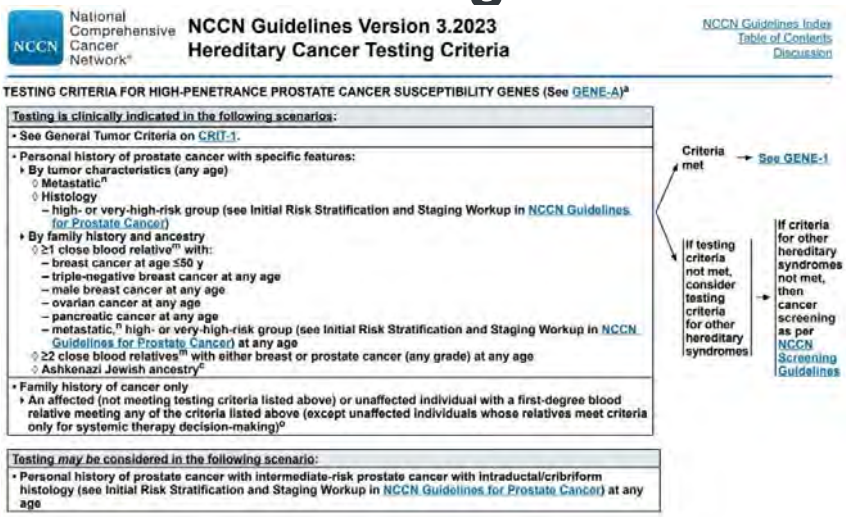
Genetic Testing Criteria



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Prostate Cancer Genes

Gene	Syndrome	Estimated Risk of Prostate Cancer	Other Cancer Risks
BRCA1, BRCA2	Hereditary Breast & Ovarian Cancer Syndrome	Up to 61%	Breast, Ovarian, Male Breast, Pancreatic
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch Syndrome	Up to 24%	Colon, Uterine, Ovarian, Stomach, Other GI, **Bladder, Renal**
HOXB13 (p.Gly84Glu variant)		Up to 60%	
CHEK2		Elevated	Breast, Colon
TP53	Li-Fraumeni Syndrome	Unknown	Breast, ACC, Sarcoma, Brain
ATM		Elevated	Breast, Pancreas

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Hereditary Breast & Ovarian Cancer Syndrome

Genes: *BRCA1, BRCA2*

Lifetime Risk for Prostate Cancer: **7-26% BRCA1**
19-61% BRCA2

Other Features

- Often more aggressive, earlier ages of onset than sporadic
- Increased risks for breast, ovarian, male breast, and pancreatic cancers, and melanoma, some studies suggest increased risk for stomach cancer

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Lynch Syndrome

Genes: *MLH1, MSH2, MSH6, PMS2, EPCAM*

Lifetime Risk for Prostate Cancer:

4.5-14%	***MLH1***
4-24%	***MSH2***
2.5-11.5%	***MSH6***
4.5-11.5%	***PMS2***

Other Features

- Earlier ages of onset than sporadic
- Mismatch repair deficient tumors
- Increased risks for colon, uterine, ovarian, pancreas, stomach, other GI, **bladder, renal** cancers

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Could it be Hereditary?

- General Population Risk of Renal Cell Cancer (RCC): 1-2%
- ~3% of RCC is Hereditary
  - Kidney cancer histology can be helpful in determining likelihood of a hereditary RCC

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Genetic Testing Criteria

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Hereditary Renal Cell Carcinoma

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

1. An individual with a close blood relative[b] with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene	→ See GENE-1
2. 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	→ Consider referral to cancer genetics professional and Refer to specific syndromes - See Hereditary RCC Syndromes Overview (HERED-RCC-2), See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: Principles of Cancer Risk Assessment and Counseling (EVAL-A) and Pedigree (EVAL-B) → See GENE-1
3. An individual whose tumors have the following histologic characteristics: • Multifocal papillary histology • 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 (TSC) criterion in the same person (See Table 1) • Succinate dehydrogenase (SDH)-deficient RCC histology[e]	→
4. An unaffected individual[c,d] with any of the following criteria: • ≥2 first- or second-degree relatives[b] with RCC (on the same side of the family) • Any first degree relative who meets the criteria in boxes 2 and 3 who is unable or unwilling to genetically test	→

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Renal Cancer Genes

Gene (and Condition name)	Typical Renal Tumor Histology	Renal Cancer Risk	Other Cancer Risks/Features
BAP1 (BAP1 tumor predisposition syndrome)	Clear cell Chromophobe	10%	Melanoma (cutaneous, uveal), Malignant mesothelioma, BCC
FH (Hereditary Leiomyomatosis and Renal Cell Carcinoma)	Type 2 Papillary	10-15%	Cutaneous and uterine leiomyomas
FLCN (Birt-Hogg-Dubé Syndrome)	Chromophobe Hybrid oncocytic tumors Papillary RCC	34%	Fibrofolliculomas, Pulmonary cysts, Spontaneous pneumothorax
MET (Hereditary Papillary Renal Cancer)	Type 1 Papillary	100%	
PTEN (Cowden Syndrome)	Papillary RCC	30-35%	Breast, Colon, Uterine, Thyroid Cancer Risk, colon polyps, macrocephaly, mucocutaneous lesions
SDHA, SDHB, SDHC, SDHD (Hereditary Paraganglioma and Pheochromocytoma Syndrome)	Clear cell Chromophobe Papillary type 2 Renal oncocytoma Oncocytic neoplasm	5-15%	Pheochromocytoma, Paraganglioma, GIST
TSC1, TSC2 (Tuberous Sclerosis Complex)	Angiomyolipoma Clear cell	2-5%	Facial angiofibromas, hypopigmented macules, shagreen patch, cortical dysplasias
VHL (von Hippel-Lindau)	Clear cell (often multifocal)	24-60%	Hemangioblastomas (retina, spine, brain), PCC, PGL, retinal angiomas, pNET, pancreas cysts, endolymphatic sac tumors

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von Hippel-Lindau (VHL) Syndrome

Genes: *VHL*
Lifetime Risk for Kidney Cancer: 24-60%

Associated with:

- hemangioblastomas of the central nervous system and retina
- pheochromocytoma
- paraganglioma of abdomen, thorax, or neck
- retinal angiomas
- endolymphatic sac tumors
- pancreatic neuroendocrine tumors
- pancreatic cysts
- cystadenomas of the epididymis and broad ligament
- renal cancer
  - clear cell histology
  - multifocal, bilateral
  - early onset

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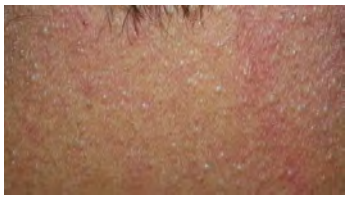
Birt-Hogg-Dubé

Genes: *FLCN*
Lifetime Risk for Kidney Cancer: 34%



Associated with:

- fibrofolliculomas
- multiple, bilateral pulmonary cysts
- spontaneous pneumothoraces
- renal tumors, variable histology:
  - hybrid oncocytic tumors, containing features of chromophobe renal cancer and oncocytoma
  - chromophobe
  - papillary renal cell carcinoma

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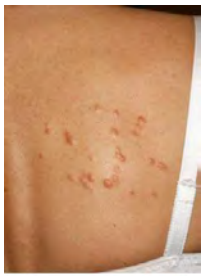
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)



Genes: *FH*
Lifetime Risk for Kidney Cancer: 10-15%

Associated with:

- cutaneous and uterine leiomyomas
- highly aggressive form of papillary kidney cancer

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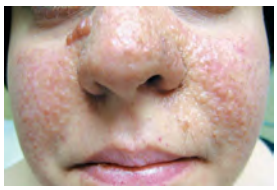
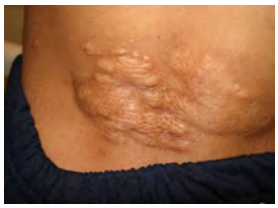
Tuberous Sclerosis Complex





Genes: *TSC1/TSC2*
Lifetime Risk for Kidney Cancer: 2-5%

Associated with:

- skin lesions including facial angiofibromas, hypopigmented macules, shagreen patch
- pulmonary lymphangioleiomyomatosis (LAM)
- cardiac rhabdomyomas
- cerebral cortex tubers
  - neurologic manifestations including epilepsy, cognitive disability and neuro-behavioral abnormalities
- bilateral, multifocal renal angiomyolipomas
- multiple renal cysts
- renal cell carcinoma

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Hereditary Paraganglioma and Pheochromocytoma Syndrome

Genes: *SDHA, SDHB, SDHC, SDHD*
Lifetime Risk for Kidney Cancer: 5-15%

Associated with:

- pheochromocytoma
- paraganglioma
- gastrointestinal stromal tumor
- renal cell carcinoma
  - variable histology
    - clear cell
    - chromophobe
    - papillary type 2
    - renal oncocytoma
    - oncocytic neoplasm
    - succinate dehydrogenase (SDH)-deficient

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Benefits of Genetic Testing

- Identifies individuals at increased risk
- Identifies individuals NOT at increased risk
- Provides early detection and prevention strategies in carriers
- Provides additional treatment options in carriers
- Relieves uncertainty and anxiety

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