Germline Testing in Hereditary Kidney Cancer Syndromes

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No disclosures.
Objectives

- **Why** to perform germline testing?
- **How** to perform germline testing?
- **In whom** to perform germline testing?
Kidney cancer: Multiple diseases

- **Clear Cell**
  - Genes: VHL, TCEB1, BAP1

- **Papillary Type 1**
  - Genes: MET

- **Chromophobe**

- **Hybrid**
  - Genes: FLCN

- **Oncocytoma**

- **Papillary Type 2**
  - Genes: FH

- **TFE3**

- **Angiomyolipoma**
  - Genes: TSC1, TSC2

- **Eosinophilic Clear/Chromophobe Hybrid**
  - Genes: SDHA, SDHB, SDHC, SDHD

- **Clear/Chromophobe PTEN**
Hereditary Kidney Cancer

- Currently 12 known syndromes that confer a predisposition to kidney cancer
- Most series suggest 5-8% of kidney cancers are associated with a known hereditary kidney cancer syndrome.
- But genetic influence likely plays a larger role...

## Known Inherited Syndromes

1. von Hippel-Lindau (VHL)  
2. Hereditary Papillary Renal Cancer (HPRC)  
3. Birt-Hogg-Dube (BHD)  
4. Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)  
5. Succinate Dehydrogenase Deficiency  
6. Microphthalmia-associated Transcription Factor RCC  
7. BAP1-associated kidney cancer  
8. Tuberous Sclerosis Complex (TSC)  
9. Chromosome 3 Translocation  
10. Hyperparathyroid -Jaw Tumor (HJT)  
11. Cowden Syndrome  
12. Familial Renal Oncocytoma (FRO)  

<table>
<thead>
<tr>
<th>Syndrome / Mutation</th>
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<tbody>
<tr>
<td>VHL</td>
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<tr>
<td>MET</td>
</tr>
<tr>
<td>FLCN</td>
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<tr>
<td>FH</td>
</tr>
<tr>
<td>SDH-B,C,D</td>
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<tr>
<td>MITF</td>
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<tr>
<td>BAP1</td>
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<tr>
<td>TSC1,2</td>
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<tr>
<td>germline balanced translocation</td>
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<tr>
<td>CDC73</td>
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<tr>
<td>PTEN</td>
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<td>mitochondrial genes</td>
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</table>
How are hereditary cases missed?

- Clinician unfamiliarity with non-renal manifestations
- Variable penetrance
- Poor family history
- Development of *de novo* mutations (~10% of hereditary patients)
Does it matter?

- Hereditary patients are treated with different paradigms.
- Identify indolent vs aggressive phenotypes
- Emphasis on organ preservation:
  - Active surveillance and partial nephrectomy
- Different pathways for systemic therapy
  - FH-deficient and SDH-deficient tumors
- Screening for the rest of family
Iceland – extensive genealogy records for “11 centuries”
1,078 RCC cases
Determine whether patients are more related to each other than controls
58% of all cases were found in families with 2 or more affected members
26% in families with 3 or more affected members.

RR of RCC with 1st degree relative: >2
80,309 monozygotic and 123,382 same-sex dizygotic twin individuals within the population-based registers of Denmark, Finland, Norway, and Sweden. Twins were followed up a median of 32 years.
10,000+ adult cancers in the TCGA dataset. TCGA specifically excluded known hereditary cancer syndromes.

Pathogenic germline alterations found in:
6% ccRCC
9% pRCC
6% chromophobe RCC
13 loci have been identified that confer increased risk of RCC, OR ~1.5 in patients of European ancestry.
Increasing emphasis in multiple malignancies

- Recent NCCN guideline changes
  - Prostate: germline testing recommended for all high-risk patients
  - Pancreatic: germline testing recommended for all patients
  - Breast: strong consider germline testing
Objectives

- **Why** to perform germline testing?
  - Syndromes are not rare
  - Can affect management

- **How** to test perform germline testing?
- **In whom** to perform germline testing?
How to test

- How many genes?
  
  Single gene
  
  confirm clinical diagnosis or known family variant
  
  lowest cost
  
  15-25 gene renal panels: established germline genes.
  
  no clear syndromic features, but suspicious family or person history
  
  Expanded panels
  
  included non-renal cancer susceptibility genes
  
  decreased signal:noise, may find more VUS → increased uncertainty
Sanger sequencing
Genetic Testing

OncoGeneDx: Renal Cancer Panel

Panel Gene List: BAP1, EPCAM*, FH, FLCN, MET, MITF*, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL

*Testing includes sequencing and deletion/duplication analysis for all genes except EPCAM (del/dup only) and MITF (only c.952G>A (p.Glu318Lys) will be analyzed and reported.)

Invitae Renal/Urinary Tract Cancers Panel

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>01361</td>
<td>Invitae Renal/Urinary Tract Cancers Panel</td>
<td>BAP1, CDC73, CDKN1C, DICER1, DIS3L2, EPCAM, FH, FLCN, GPC3, MET, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SMARCA4, SMARC81, TP53, TSC1, TSC2, VHL, WT1</td>
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<td>01361.1</td>
<td>Add-on preliminary-evidence genes</td>
<td>BUB1B, CEP57, MITF, PALB2, SDHA, SDHD</td>
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</table>
Testing considerations

- Genetic counselors: high demand, limited supply – may face wait times
- Cost – in U.S., variable insurance coverage. Need to establish risk – 3 generation pedigrees
- Implications
  - Insurability – health and life insurance
  - Screening for family members
  - Incidental findings
Objectives

- **Why** to perform germline testing?
- **How** to perform germline testing?
  - In coordination with a genetic counselor
  - Renal panel with known germline-altered genes for most suspected patients

**In whom** to perform germline testing?
Hereditary Kidney Cancer

- When to evaluate:
  - Feature of genetic syndrome
  - Early onset (before age 46)
  - Family history, especially first-degree relative
  - Bilateral and/or multifocal
  - Advanced disease
  - Rare histology
von Hippel-Lindau Disease

- VHL is a hereditary, multi-organ cancer syndrome
- Germline alterations of *VHL*
- AD inheritance
- 1:36,000
von Hippel-Lindau Disease

**BRAIN**
- Cerebellar hemangioblastoma

**EYES**
- Retinal angiomata

**EARS**
- Endolymphatic sac tumors

**SPINAL CORD**
- Spinal cord hemangioblastoma

**ADRENAL GLANDS**
- Pheochromocytoma

**EPIPHYSIS**
- Multiple pancreatic cyst
- Pancreatic neuroendocrine tumors

**KIDNEYS**
- Renal hemangioblastoma
- Renal cell carcinoma
- Multiple renal cysts

**FEMALE GENITALIA**
- Bilateral papillary cystadenomas of the broad ligament

**MALE GENITALIA**
- Bilateral papillary cystadenoma of the epididymis
- Epidyelmal Cysts

CNS Hemangioblastomas
von Hippel-Lindau Disease

- BRAIN: Clear cell hemangioblastoma
- EYES: Retinal angiomas
- EARS: Endolymphatic sac tumors
- SPINAL CORD: Spinal cord hemangioblastoma
- ADRENAL GLANDS: Pheochromocytoma
- INTESTINES: Multiple pancreatic cysts, Pancreatic neuroendocrine tumors
- KIDGENS: Renal hemangioblastomas, Renal cell carcinoma, Multiple renal cysts
- FEMALE GENITALIA: Bilateral papillary cystadenomas of the broad ligament
- MALE GENITALIA: Bilateral papillary cystadenoma of the epididymis, Epididymal Cysts
von Hippel-Lindau Disease

**Endolymphatic Sac Tumors (ELST)**

- **Brain**: Cerebellar hemangioblastoma
- **Eyes**: Retinal angiomata
- **Ears**: Endolymphatic sac tumors
- **Spinal Cord**: Spinal cord hemangioblastoma
- **Adrenal Glands**: Phaeochromocytoma
- **Kidneys**: Renal hemangioblastoma, Renal cell carcinoma, Multiple renal cysts
- **Female Genitalia**: Bilateral papillary cystadenomas of the broad ligament
- **Male Genitalia**: Bilateral papillary cystadenoma of the epididymis, Epididymal Cysts
von Hippel-Lindau Disease

- **BRAIN**: Glioblastoma multiforme
- **EYES**: Retinal angiomata
- **EARS**: Endolymphatic sac tumors
- **SPINAL CORD**: Spinal cord hemangioblastoma

- **ADRENAL GLANDS**: Pheochromocytoma
- **EXYNES**: Multiple pancreatic cysts, Pancreatic neuroendocrine tumors
- **KIDNEYS**: Renal hemangioblastoma, Renal cell carcinoma, Multiple renal cysts
- **FEMALE GENITALIA**: Bilateral papillary cystadenomas of the broad ligament
- **MALE GENITALIA**: Bilateral papillary cystadenoma of the epididymis, Epididymal Cyst

Pheochromocytomas/Paragangliomas
von Hippel-Lindau Disease

BRAIN
- Cerebellar hemangioblastoma

EYES
- Retinal angiomata

EARS
- Endolymphatic sac tumors

SPINAL CORD
- Spinal cord hemangioblastoma

ADRENAL GLANDS
- Phaeochromocytoma

EYES
- Multiple pancreatic cysts
- Pancreatic neuroendocrine tumors

KIDNEYS
- Renal hemangioblastoma
- Renal cell carcinoma
- Multiple renal cysts

FEMALE GENITALIA
- Bilateral papillary cystadenomas of the broad ligament

MALE GENITALIA
- Bilateral papillary cystadenoma of the epididymis
- Epidyimal Cysts

Pancreatic Cyst
Pancreatic Neuroendocrine Tumors
von Hippel-Lindau Disease

- **Brain**: Cerebellar hemangioblastoma
- **Eyes**: Retinal angiomata
- **Ears**: Endolymphatic sac tumors
- **Spinal Cord**: Spinal cord hemangioblastoma
- **Adrenal Glands**: Pheochromocytoma
- **Pancreas**: Multiple pancreatic cysts, Pancreatic neuroendocrine tumors
- **Kidneys**: Renal hemangioblastoma, Renal cell carcinoma, Multiple renal cysts
- **Female Genitalia**: Bilateral papillary cystadenomas of the broad ligament
- **Male Genitalia**: Bilateral papillary cystadenoma of the epididymis, Epididymal Cyst

**Kidney cysts**
Renal cell carcinoma
von Hippel-Lindau Disease

- **BRAIN**
  - Cerebellar hemangioblastoma

- **EYES**
  - Retinal angiomata

- **EARS**
  - Endolymphatic sac tumors

- **SPINAL CORD**
  - Spinal cord hemangioblastoma

- **ADRENAL GLANDS**
  - Pheochromocytoma

- **KIDNEYS**
  - Renal hemangioblastoma
  - Renal cell carcinoma
  - Multiple cysts

- **FEMALE GENITUALIA**
  - Bilateral papillary cystadenomas of the broad ligament

- **MALE GENITALIA**
  - Bilateral papillary cystadenoma of the epididymis
  - Epididymal Cyst

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Cystadenomas of the broad ligament
Cystadenomas of the epididymis
Hereditary Leiomyomatosis and Renal Cell Carcinoma
Birt Hogg Dubé
Kidney + other malignancies

- VHL - pancreas, CNS
- MITF – melanoma
- BAP1 – melanoma, mesothelioma
- Cowden’s/PTEN- breast, endometrial, thyroid, colorectal, melanoma
Defining Early-Onset Kidney Cancer: Implications for Germline and Somatic Mutation Testing and Clinical Management

Shuch B, JCO 2014
Enriched population screening

Bilateral and/or Multifocal (BMF) RCC

Early Onset (EO) RCC (age of diagnosis < 46)

59 Patients

28 Patients

38 Patients

10 Patients

16 Patients

12 Patients

Familial Renal Cancer (FRC)

No Enrichment Factor

28 Patients

207 patients referred with no clinical or genetic diagnosis of heredity syndrome

Ball MW et al AUA 2019
Results

- Overall positive results (17%)
  - Early onset (19.5%)
  - FRC (35.2%)
  - BMF (21%)
- 15% has VUS
Advanced disease

267 unscreened patients presenting with stage III or IV RCC at MSK

Carlo et al, JAMA Oncology
Objectives

- **Why** to perform germline testing?
- **How** to perform germline testing?
  - **In whom** to perform germline testing?
    - Feature of genetic syndrome
    - Early onset (before age 46)
    - Family history, especially first-degree relative
    - Bilateral and/or multifocal
    - Advanced disease
    - Rare histology
Conclusions

- Clinicians treating kidney cancer will see hereditary syndrome patients (whether you know it or not)
- Early onset, bilateral/multifocal disease, family history should be triggers for genetic counseling.
- Also consider: rare histology, other malignancies