Hereditary Genitourinary Cancers & Genitourinary Cancer Screening

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Disclosures

- None

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Objectives

- Review genitourinary cancer incidence, mortality and screening data.
- Identify patient populations who would benefit from high-risk genitourinary cancer screening and management.
- Discuss the evidence and rationale supporting clinical recommendations for genitourinary cancer prevention and screening methods

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Figure 3. Leading Sites of New Cancer Cases and Deaths – 2023 Estimates

Estimated New Cases

Male			Female		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All sites	**1,010,310**		**All sites**	**948,000**	

Estimated Deaths

Male			Female		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All sites	**322,080**		**All sites**	**287,740**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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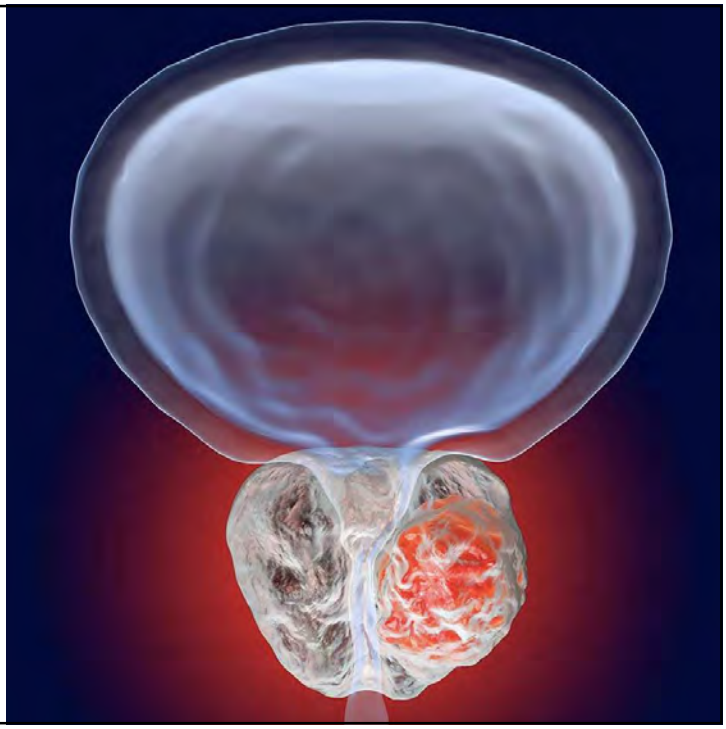
Prostate



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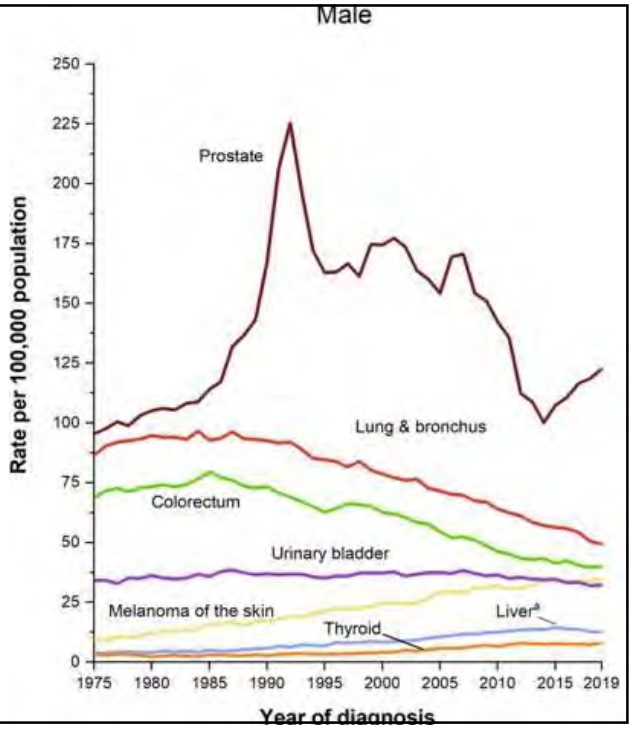
Prostate Cancer

- Prostate Specific Antigen (PSA)
  - Enzyme secreted by the prostate which liquifies semen
  - Prostate specific, but not cancer specific.
  - Normal level is age dependent
  - PPV increase with elevation, however no absolutes



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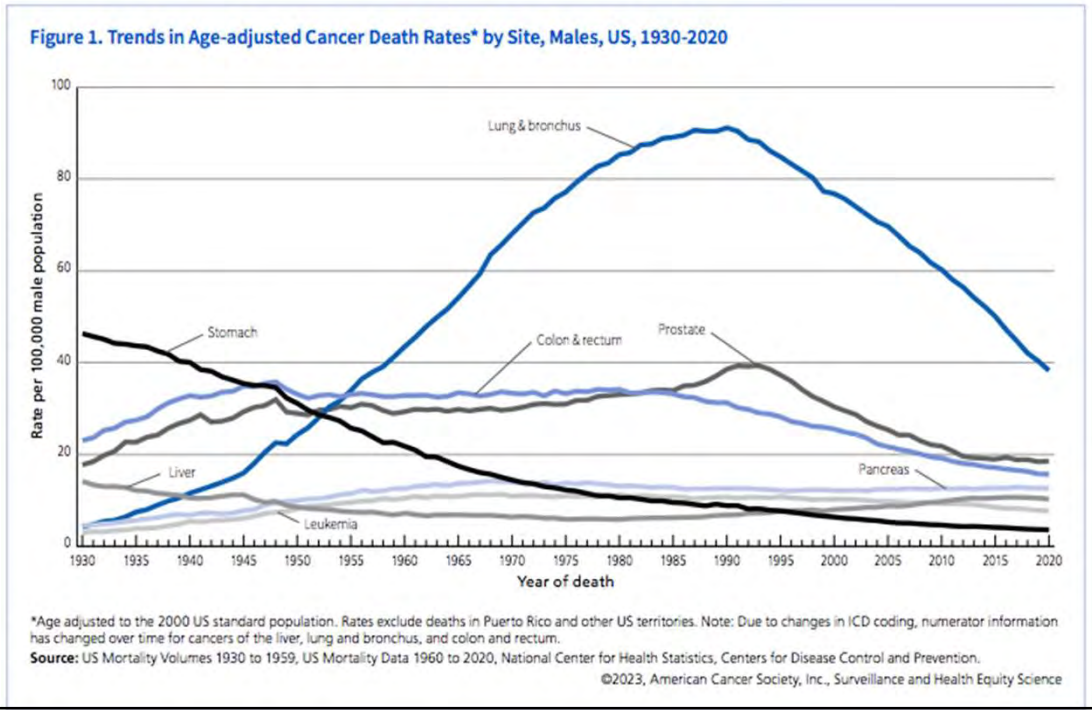

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PSA Screening Guidelines

- Common themes
  - Shared decision making
  - Average risk vs high risk
  - Greatest benefit in men with 10 year+ life expectancy
- American Urologic Association (2018)
  - Average risk men 55-69 yo
  - Every other year

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Population Based Screening Studies

- ERSPC
  - Benefit to prostate cancer screening
  - # to screen = 293-1055
  - # to treat = 12- 37
- PLCO
  - No benefit to screening
  - High prescreening rates and high contamination rates (74%)

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Limitations of ERSPC and PLCO

- Low inclusion of high risk population
- Poor diagnostic techniques
  - Automatic biopsy for PSA above threshold
  - MRI and MRI fusion biopsy
- Failure to understand individual and selective treatment
  - Increasing prevalence of active surveillance today

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High Risk Populations

- Family history
  - Breast or prostate
  - RR 2-1-2.5 if first degree relative diagnosed with prostate cancer <60 yo
- African ancestry
  - 60% increased incidence and 36-39% increased mortality compared to White individuals
  - Not highly included in screening studies
- Genetic syndromes
  - DNA repair genes: BRCA2, ATM, CHECK2
    - BRCA1, RAD51D, PALB2, ATR, NBN, PMS2, GEN1, MSH2, MSH6, RAD51C, MRE11A, BRIP1, FAM175A

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Guidelines for High-Risk Population

- Insufficient evidence to definitively inform guidelines
- NCCN Guidelines
  - Family history: consider starting 10 years prior to age of diagnosis for those with first degree relative diagnosed at < 60 yo
  - African ancestry: consider starting at age 40 and performing annually
  - Genetic Mutations
    - BRCA2: starting at age 40 and performing annually
    - Others: also reasonable to consider starting at age 40 and performing annually.

NCCN Guidelines. Prostate Cancer Early Detection. Version 1.2023.

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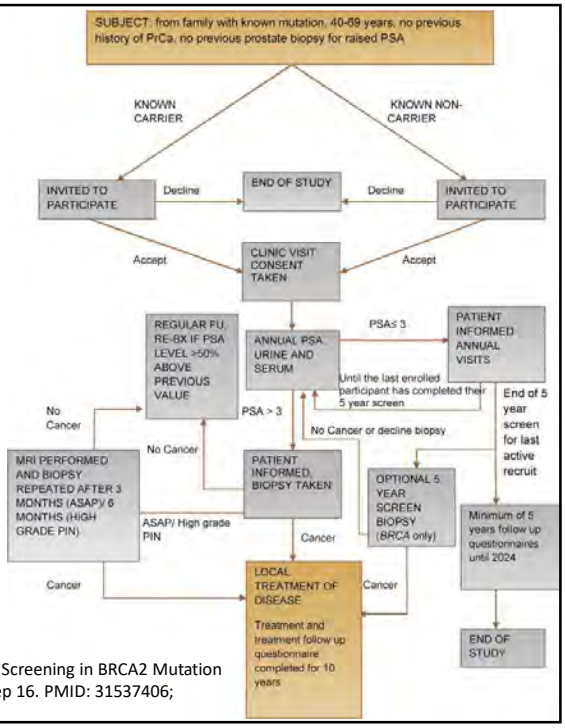
BRCA: IMPACT Study

- Prospective study of PSA screening in BRCA1/2 vs control
- Patient's screened annually with PSA
- Prostate biopsy performed if PSA >3



Page EC, et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. Eur Urol. 2019 Dec;76(6):831-842. doi: 10.1016/j.eururo.2019.08.019. Epub 2019 Sep 16. PMID: 31537406; PMCID: PMC6880781.

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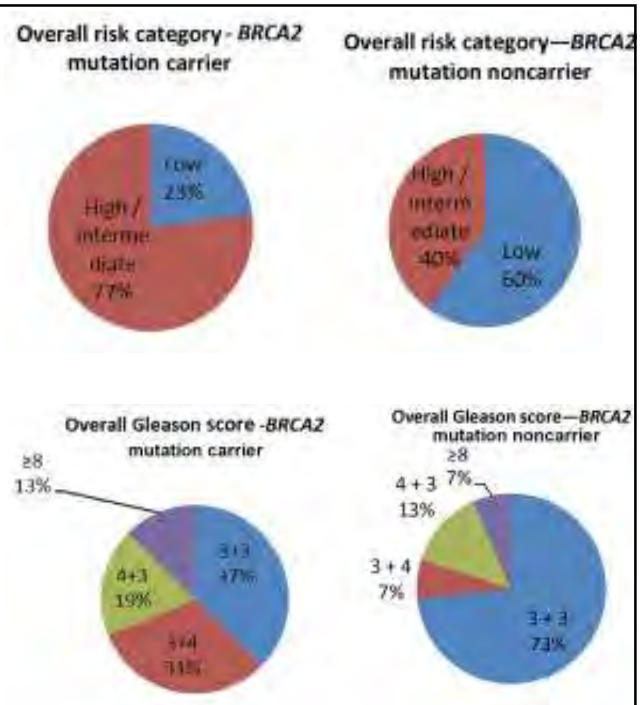
BRCA: IMPACT Study

- BRCA2 carriers
  - Higher cancer incidence (19.04 per 1000 py vs 12, *p*= 0.03)
  - Diagnosed at a younger age (61 vs 64 yr; *p* = 0.04)
  - More likely to have clinically significant disease (77% vs 40%; *p* = 0.01)
- BRCA1 carriers
  - No difference in age at diagnosis or tumor characteristics



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Kidney

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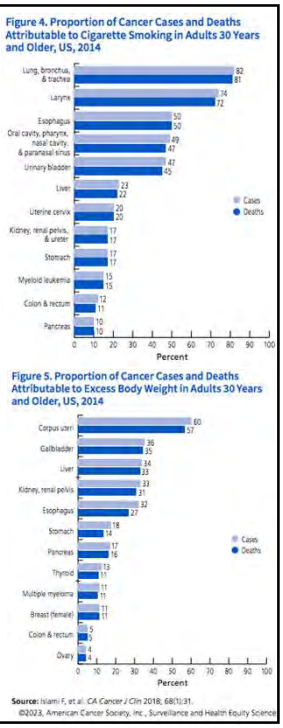
Kidney Cancer

- Incidence: 81,800 new cases in US in 2023
  - Long term increase in incidence due to increased incidental detection of asymptomatic tumors
  - Increased by 1% per year from 2010-2019
- Mortality: 14,890 deaths in US in 2023
  - Declining since 1990s
  - Decreasing by 2% per year from 2013-2020
- Risk Factors
  - Smoking
  - Obesity
- Screening: none in average risk individuals



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Hereditary RCC

- 3-5% of RCCs
- Earlier age of presentation
- More likely to be multifocal or bilateral

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Syndrome/Gene	Common Histologies	Inheritance Pattern Major Clinical Manifestations	Other Specialists Involved in Screening
von Hippel-Lindau (VHL)/ *VHL* gene	Clear cell	• Autosomal dominant • See Table 2	• Neurosurgery • Ophthalmology • Audiology • Endocrinology • Endocrine surgery
Hereditary papillary renal carcinoma (HPRC)/*MET* gene	Type 1 papillary	• Autosomal dominant • Multifocal, bilateral renal cell tumors	• Nephrology
Birt-Hogg-Dubé syndrome (BHDS)/*FLCN* gene[1,2]	Chromophobe, hybrid oncocytic tumors, papillary RCC	• Autosomal dominant • Cutaneous fibrofolliculoma or trichodiscoma, pulmonary cysts, and spontaneous pneumothorax	• Pulmonology • Dermatology
Tuberous sclerosis complex (TSC)/*TSC1*, *TSC2* genes	Angiomyolipoma, clear cell	• Autosomal dominant • See Table 1	• Neurology • Dermatology
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)/*FH* gene	HLRCC or FH-associated RCC/ type 2 papillary	• Autosomal dominant • Leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors. PET-positive adrenal adenomas	• Gynecology • Dermatology
BAP1 tumor predisposition syndrome (TPDS)/*BAP1* gene[3,4]	Clear cell, chromophobe	• Autosomal dominant • Melanoma (uveal and cutaneous), kidney cancer, mesothelioma	• Dermatology • Ophthalmology • Thoracic oncology
Hereditary paraganglioma/ pheochromocytoma (PGL/ PCC) syndrome/*SDHA/B/ C/D* genes	Clear cell (not usually *SDHB*), chromophobe, papillary type 2, renal oncocytoma, oncocytic neoplasm	• Autosomal dominant • Head and neck PGL and adrenal or extra-adrenal PCCs, gastrointestinal stromal tumors (GISTs)	• Endocrine • Endocrine surgery

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Table 1: Features of Tuberous Sclerosis (TSC)

Major Features	Minor Features
• Renal angiomyolipoma[1,2] • Cardiac rhabdomyoma • Cortical dysplasias, including tubers and cerebral white matter migration lines • Angiofibromas (≥3) or fibrous cephalic plaque • Hypomelanotic macules (3 to >5 mm in diameter) • Lymphangioleiomyomatosis (LAM)[1] • Multiple retinal nodular hamartomas • Shagreen patch • Subependymal giant cell astrocytoma (SEGA) • Subependymal nodules (SENs) • Ungual fibromas (≥2)	• Multiple renal cysts • "Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs) • Dental enamel pits (>3) • Intraoral fibromas (≥2) • Nonrenal hamartomas • Retinal achromic patch

Table 2: Features of Von Hippel-Lindau (VHL) Disease

Major Features	Minor Features
• Hemangioblastomas of the retina, spine, or brain • Clear cell RCC (ccRCC) diagnosed <40 years of age or multiple/ bilateral ccRCC tumors diagnosed at any age • PCCs • PGL of abdomen, thorax, or neck • Retinal angiomas	• Endolymphatic sac tumors • Papillary cystadenomas of the epididymis or broad ligament • Pancreatic serous cystadenoma (>1) • Pancreatic neuroendocrine tumor (pNET) or multiple pancreatic cysts (>1)

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Principles of Screening

- Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.
- Whenever possible, screening should be coordinated with another specialist involved in patient's care.
- Females of childbearing age who are planning conception should consider renal imaging prior to pregnancy.
- If there is a family member with an early diagnosis, screening should begin 10 y before earliest age of diagnosis in family member.
- CT of the abdomen can be used for surgical planning but should be limited if possible for surveillance due to lifetime radiation exposure for hereditary syndromic patients. MRI preferred for all screening.
- Imaging frequency would be increased once lesions are detected based on growth rate and size of lesion(s).

NCCN Kidney Cancer Guidelines. Version 4.2023

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NCCN Screening Recommendations

Syndrome/Gene	Starting Age	Frequency
BAP1	30	2y
BHDS	20	3y
HLRCC	8-10	1y
HPRC	30	1-2
PGL/PCC	12	4-6
TSC	12	3-5
VHL	15	2y

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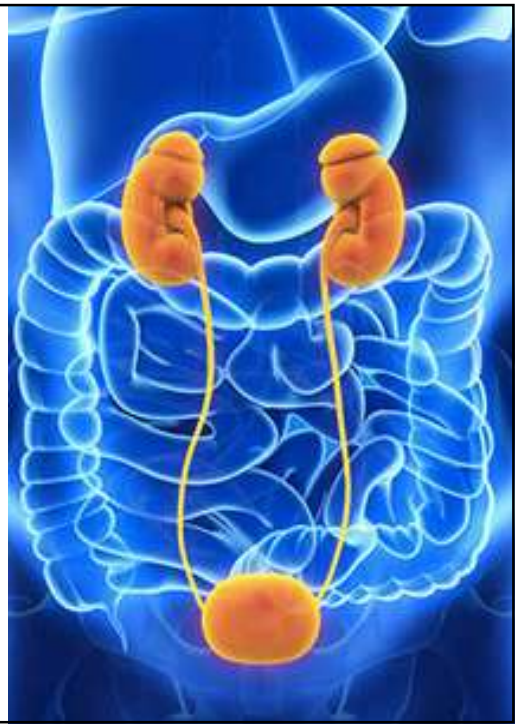
Urothelial Cell Carcinoma



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Urothelial Cell Carcinoma

- Primary risk factors: smoking, chemical/dye exposure
- No screening guidelines in patients at average risk or high risk

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Urothelial Cell Carcinoma

- Ideal Screening Test: high sensitivity, high specificity, cost effective
- Options and their pitfalls
  - UA with micro: low specificity, low predictive value
    - Jubber, et al meta-analysis of patients with microscopic hematuria
      - 0-16% for bladder cancer
      - 0-3.5% for upper tract urothelial cancer
  - Cytology: low sensitivity, costly
  - Biomarkers: low sensitivity, costly
  - Cystoscopy: invasive, costly

Jubber I, Shariat SF, Conroy S, Tan WS, Gordon PC, Lotan Y, Messing EM, Stenzl A, Rhijn BV, Kelly JD, Catto JWF, Cumberbatch MG. Non-visible haematuria for the Detection of Bladder, Upper Tract, and Kidney Cancer: An Updated Systematic Review and Meta-analysis. Eur Urol. 2020 May;77(5):583-598. doi: 10.1016/j.eururo.2019.10.010. Epub 2019 Nov 30. PMID: 31791622.

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Lynch Syndrome

- Increased risk of upper tract urothelial cell carcinoma
  - Especially males with MSH2 pathogenic variant

Pathogenic Variant	Estimated Age at Presentation	Cumulative Risk through Age 80
MLH1	59-60	0.2-5%
MSH2	54-61	2.2-28%
MSH6	65-69	0.7-5.5%
PMS2	-	≤1-2.4%

Dominguez-Valentin M, Sampson J, Seppälä T, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15-25.

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Lynch Syndrome

- "Surveillance may be considered in selected individuals such as with a family history of urothelial cancer. Surveillance options may include annual urinalysis starting at age 30–35 years. However, there is insufficient evidence to recommend a particular surveillance strategy."
- Counseling: decrease modifiable risk factors

NCCN Genetic/familial high-risk assessment: colorectal. Version 2.2022

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Questions?

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