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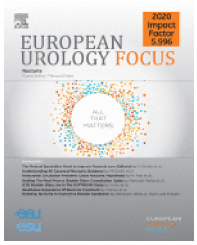

Guidelines

# Guidelines on Germline Testing for Urologic Tumor Syndromes

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**Abstract**

In the expanding precision medicine landscape, along with improvements in and the availability of testing, the use of genetics in the evaluation and treatment of patients has increased significantly. Multiple urologic cancers in different organ systems associated with an inherited gene mutation have been described. As these mutations can impact screening and treatment decisions for patients and their families, it is important for providers to be familiar with the current guidelines for germline testing. Here we summarize the current guidelines regarding germline testing for patients with suspected urologic tumor syndromes.

*Patient summary:* Several cancers of the genitourinary tract can be associated with inherited genetic mutations. Knowledge of when to test for these mutations has implications for both treatment and screening of patients and their family members at risk of genitourinary cancers.



## 1. Introduction

Beginning with identification of the von Hippel Lindau gene in the 1990s, the landscape of precision urologic oncology has evolved rapidly. Here we summarize the current international guidelines relating to germline testing for urologic tumor syndromes. These guidelines have implications for both screening of potentially affected individuals and targeted treatment in the ever-expanding landscape of precision medicine and targeted therapies. The initial step in identifying appropriate candidates for testing is to take a comprehensive history, covering the patient's medical history in addition to a three- to four-generation pedigree with relevant cancer details (at a minimum: age at diagnosis, cause of death/age of death, and any prior genetic testing) [1]. It is important to note that appropriate referral to a certified genetic counselor should be made, especially for patients for whom a pathogenic variant has been identified, to help inform possible cascade testing for family members. Referral is also important for patients with a positive family history when no pathogenic variant or a variant of unknown significance is identified to guide additional testing or follow-up recommendations.

## 2. Prostate cancer

Second only to kidney cancer, knowledge of germline mutations in prostate cancer (PC) can lead to actionable treatments for patients, with several targeted therapies recently approved for use in PC. The European Association of Urology (EAU), European Society of Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and American Urological (AUA)/American Society of Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO) provide recommendations for germline testing in prostate cancer. The EAU guideline includes a strong statement that

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**Table 1 – Current recommendations for germline testing in PC**

| Group | Recommend/consider | Guidelines | LE/strength |
|---|---|---|---|
| NCCN [4] | Recommend | Men with metastatic, regional (node-positive), high-risk, or very high-risk localized PC | 2a[a] |
| | Recommend | Men with positive FHx | 2a |
| | | ≥1 first-, second, or third-degree relatives with: | |
| | | Breast, colorectal, or endrometrial cancer at age ≤50 yr | |
| | | Male breast cancer, ovarian cancer, or exocrine pancreas cancer at any age | |
| | | Metastatic, regional, very high-risk, or high-risk PC at any age | |
| | | ≥1 first-degree relative with PC at age <60 yr | |
| | | ≥2 first-, second-, or third-degree relatives with breast cancer or PC (except localized GG 1 disease) at any age | |
| | | ≥3 first- or second-degree relatives with LS-related cancers, especially at age <50 yr (colorectal, endometrial, gastric, ovarian, UTUC, glioblastoma, biliary tract, small intestinal) | |
| | Recommend | Men with known FHx of cancer risk mutation, especially *BRCA1/2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2/6*, *PMS2*, *EPCAM* | 2a |
| | Recommend | Men of Ashkenazi Jewish ancestry | 2a |
| | Recommend | Men with a personal history of breast cancer | 2a |
| | Consider | Men with intermediate-risk PC with intraductal/cribriform histology | 2a |
| | Consider | Men with PC and a personal history of cancer (exocrine pancreas, colorectal, gastric, melanoma, pancreatic, UTUC, glioblastoma, biliary tract, small intestinal) | 2a |
| EAU [2] | Consider | Men with metastatic PC | Weak |
| | Consider | Men with high-risk PC with a family member with a PC Dx at age <60 yr | Weak |
| | Consider | Men with multiple family members with a PC Dx at age <60 yr or a family member who died of PC | Weak |
| | Consider | Men with FHx of high-risk mutations or multiple cancers on the same side of the family | Weak |
| ESMO [3] | Recommend | Germline testing for *BRCA2*/DDR genes in men with FHx of cancer | Strong/moderate |
| | Consider | Germline testing for *BRCA2*/DDR genes in men with metastatic PC | Strong/moderate |
| | Recommend | Men with pathogenic mutations in cancer risk genes on tumor testing | Strong |
| AUA/ASTRO: clinically localized PC [5] | Recommend | Assessment of patient and tumor factors to offer testing and to include mutations known to be associated with aggressive PC and/or known to have implications for treatment (strong FHx of PC; strong personal/FHx of related cancers; known FHx of cancer risk mutation; Ashkenazi Jewish ancestry; adverse tumor characteristics) | Expert opinion |
| AUA/ASTRO/SUO: advanced PC [6] | Recommend | Men with mHSPC | Expert opinion |
| | Recommend | Men with mCRPC | |
| Philadelphia Consensus 2017/ 2019 [7,8] | Recommend | Men with mHSPC or mCRPC | Expert opinion |
| | Consider | Men with nonmetastatic PC with Ashkenazi Jewish ancestry, ≥T3a disease, intraductal/ductal pathology, GG ≥4 | Expert opinion |
| | Recommend | Men with 1 brother/father or ≥2 male relatives with PC at age <60 yr any of whom died of PC or had metastatic PC | Expert opinion |
| | Consider | Men with ≥2 HBOC or LS-related cancers in any relative on the same side of the family (especially if Dx at age <50 yr) | Expert opinion |
| | Recommend | Men with tumor sequencing showing mutations in cancer risk genes, especially with a family history | Expert opinion |

ASTRO = American Society of Radiation Oncology; AUA = American Urological Association; DDR = DNA damage repair; Dx = diagnosis; EAU = European Association of Urology; ESMO = European Society of Medical Oncology; FHx = family history; GG = grade group; HBOC = hereditary breast and ovarian cancer; LE = level of evidence; LS = Lynch syndrome; NCCN = National Comprehensive Cancer Network; PC = prostate cancer; mCRPC = metastatic castrate-resistant PC; mHSPC = metastatic hormone-sensitive PC; SUO = Society of Urologic Oncology; UTUC = upper tract urothelial carcinoma.

[a] LE/strength 2a: "Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate".

genetic counseling is required before and after undergoing germline testing. The guideline then provides several clinical scenarios in which testing should be considered. These include men with metastatic disease, men with high-risk PC and a family member with PC at age <60 yr, men with multiple family members diagnosed with clinically significant PC at age <60 yr or any family member who died from PC, and men with a family history of a high-risk germline mutation or multiple cancers on the same side of the family [2]. ESMO recommends germline testing for carriers of a *BRCA2* mutation and patients with mutations in other DNA damage repair genes and a family history of cancer, and all patients with metastatic disease. ESMO also recommends referral for genetic counseling and testing for patients with pathogenic mutations identified via testing of tumor tissue [3]. The NCCN recommends germline testing for patients with metastatic, regional (node-positive), high-risk and very high-risk localized prostate cancer. In addition, the NCCN recommends testing for patients with Ashkenazi Jewish ancestry, a known family history of a familial cancer risk mutation, or a family history of certain cancers. Table 1 provides more details regarding the definitions of a positive family history according to the NCCN panel. Clinicians can consider germline testing for patients with prostate cancer with intermediate-risk tumors with intraductal/cribriform histology and patients with a per-

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sonal history of certain cancers (pancreas, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal) [4].

The AUA and ASTRO recently updated their guidelines on localized prostate cancer, with the addition that clinicians should perform an assessment of patient and tumor risk factors that may guide a decision to offer germline testing. Indications listed in these guidelines for testing in this setting align with several of the NCCN recommendations and include a strong family history of prostate cancer or personal/family history of related cancers, known family history of a cancer risk mutation, Ashkenazi Jewish ancestry, and adverse tumor characteristics [5]. The AUA/ASTRO/SUO joint guideline for advanced prostate cancer recommends germline testing for patients with metastatic hormone-sensitive prostate cancer regardless of age and family history and to identify DNA damage repair deficiency mutations and microsatellite instability status that may inform prognosis for patients with metastatic castrate-resistant prostate cancer and counseling regarding family risk [6].

First convened in 2017, the Philadelphia Prostate Cancer Consensus was a multidisciplinary meeting of 71 thought leaders in multiple disciplines and key stakeholders to provide a framework for genetic evaluation of patients with suspected hereditary prostate cancer [7]. A second meeting was held in 2019 to establish consensus on a recommended implementation framework to help in ensuring adequate access to genetic testing and to update the consensus recommendations for germline testing [8]. The panel recommendations are summarized in Table 1.

## 3. Kidney cancer

There are numerous hereditary tumor syndromes that increase the risk of kidney cancer with implications for screening and both surgical and systemic treatments [9]. The AUA (expert opinion), NCCN (level 2a), and EAU (strong) guidelines recommend referral for consideration of germline testing for all patients aged ≤46 yr with renal cancer, those with multifocal/bilateral renal masses, those with a personal/family history suggestive of a renal cancer syndrome, those with a first- or second-degree relative with a renal cancer or known diagnosis of a familial cancer syndrome, and patients with pathology suggestive of histologic findings [10,11]. The NCCN lists the histologic features that should raise suspicion, including multifocal papillary, fumarate hydratase–deficient tumors, multiple chromophobe/oncocytomas or hybrid tumors, angiomyolipomas with one additional tuberous sclerosis complex criterion, and tumors with succinate dehydrogenase deficiency [11].

Similar to the prostate cancer consensus meetings, a similar group was convened in 2019 to provide a framework for genetic assessments in patients with hereditary renal cancer. Many consensus recommendations based on expert opinion align with those of the AUA and NCCN related to multifocal tumors, family members with syndromic manifestations suggestive of a renal cancer syndrome, documented history of a renal cancer syndrome, and histology suggestive of renal cancer syndromes. Of note, consensus was not reached regarding a specific age at which to recommend genetic testing [12].

## 4. Urothelial carcinoma

While genetic alterations are quite common in bladder cancer, apart from upper tract urothelial carcinoma (UTUC) and its association with hereditary nonpolyposis colorectal cancer (known as Lynch syndrome), no tumor syndromes that increase the risk of a lower tract urothelial carcinoma have specifically been identified. For patients with upper tract tumors, the NCCN bladder cancer guidelines [13] recommend referral for germline testing for Lynch syndrome in patients who are <60 years of age at presentation or with a personal history of colon and/or endometrial cancer (level 2a). Further criteria for evaluation of Lynch syndrome are expanded in the colorectal NCCN guidelines, with testing recommended for patients with a known pathogenic variant in the family, personal history of a tumor with mismatch repair deficiency diagnosed at any age, and a family history of first-, second-, or third-degree relatives with Lynch syndrome–related cancers. The NCCN provides a detailed framework for referral for genetic testing on the basis of tumor tissue screening results for microsatellite instability or gene mutations suggestive of Lynch syndrome [14]. The EAU guidelines [15] provide comparable recommendations on germline testing for individuals with UTUC presenting at age <60 yr, those with a personal history of a Lynch syndrome–related cancer, a first-degree relative with Lynch related cancer at age <50 yr, two first-degree relatives with a Lynch syndrome–related cancer regardless of age, and patients with sporadic UTUC with positive immunohistochemistry staining suggestive of a mismatch repair gene mutation (weak).

## 5. Conclusions

In general, the guidelines share several recommendations for germline testing across several tumor types. Common recommendations for germline testing include patients diagnosed at a young age, patients with a family history suggestive of a hereditary cancer syndrome, patients with aggressive or metastatic disease, and patients whose tumor testing suggests or demonstrates a mutation in a pathogenic gene. Given the 2020 approval of PARP inhibitors for prostate cancer, this urologic cancer currently has the greatest focus in the international guideline landscape relating to germline testing.

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