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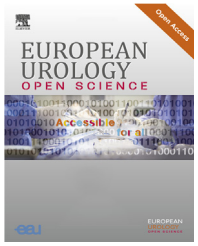

European Association of Urology

Brief Correspondence

Hereditary and Familial Traits in Urological Cancers and Their Underlying Genes

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Abstract

Early recognition of hereditary urological cancers may influence diagnostic and therapeutic decision-making, and potentially alter the fate of patients and family members. Here, we introduce readers to the current knowledge on germline genetic testing and clinical practice in prostate, bladder, renal, and testicular carcinoma. Considering all urological cancer patients, routine inquiries about familial cancer history should become a standard practice in clinical settings. If suspicion arises, patients can opt for two avenues: referral to genetic counseling or undergoing genetic tests after consultation with the treating urologist.

Patient summary: Tumors of the urogenital tract (prostate, kidney, bladder, and testes) can sometimes be related to genetic mutations that are present in all the cells of the body. Such mutations can be inherited and run in families. Therefore, it is relevant to obtain information on the incidence of all cancers in the family history. The information obtained may initiate genetic testing, leading to the identification of mutations that are related to cancer in the current or next generation. In addition, these mutations may offer alternative treatment options for patients.

1. Introduction

Familial cancer may be defined through occurrence of the same cancer in two or more genetically related individuals. Hereditary cancer is a high-risk familial cancer for which predisposing genes have been identified and/or the inheritance pattern is Mendelian. For the management of hereditary cancers, it is essential to identify individuals and families at risk through the patient's family history or suggestive clinical history relating to age at diagnosis, multiple primary cancers, or tumor phenotype [1–4]. While ascertainment of a family history is an important part in most management recommendations, panel sequencing may be an additional diagnostic tool that may detect pathogenic mutations independently [5]. While the need for action regarding high-risk families is generally accepted and some management procedures are in place, there are no consensus guidelines for the much larger group of families with low penetrance aggregation (penetrance is the likelihood of being affected in mutation carriers). Even though guidelines from professional organizations on the management of low-risk familial cancer are lacking, familial and genetic risks have been considered in prostate cancer (PCa) screening recommendations [6]. Age-specific familial risks have been used to define the antedated starting age for population screening of prostate and breast cancers [7,8]. A PCa

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family history has been incorporated into risk prediction tools [9].

In this introductory chapter, we review empirical familial risks and proportions as guidance to the landscape of familial urological cancer. The focus is on concordant (same) cancer as this is the most common familial clustering. However, even certain discordant cancers cluster, but the risks tend to be low, and the significance would not be obvious in the clinical setting [10].

1.1. Familial risks

As family members share both the genes and the environment, it is a priori not clear what the contribution of each is to familial cancer. The question has been approached by analyzing cancer risks between spouses who have lived a long time together. The results showed no correlation of risk between spouses for most cancers, particularly for those not related to tobacco smoking or solar exposure [11,12]. For sex-specific cancers, environmental sharing has been assessed among siblings, comparing those born close with those born far apart, presuming that a large age difference translates to low environmental sharing; no large differences were noted [13]. These data suggest that familial cancers are mainly due to germline genetics. In case of PCa, detection of an insignificant cancer due to the initiation of screening of spouses might contribute unintentionally to the incidence of familial cancers [14].

Medical staff working on familial cancer are well aware of the difficulty of obtaining a reliable family history even between first-degree family members. That is why the Swedish Family-Cancer Database (FCD) has been a unique resource, in which practically the whole nation has been organized in families and all their cancers can be obtained from the Swedish Cancer Registry. Family relationships are obtained from complete national registers, and thus the data from FCD have no reporting issues that often bias interview studies [15]. The present data are collected from a 2021 publication for which the source population covered 16.8 million individuals with clinical cancer data and other detailed personal information from 1958 through 2016 [16].

Table 1 lists familial relative risks as standardized incidence ratios (SIRs; standardized on age, sex, period, region, and socioeconomic status) calculated for offspring of affected parents or siblings. SIRs are shown when one or more than one first-degree family member (proband) was diagnosed with concordant cancer. Familial proportion shows the fraction of familial cancer of all defined cancers in the offspring generation. For example, in Sweden in one generation, of all families with PCa, 26.4% have at least two men diagnosed with PCa.

The familial risk for PCa was 2.2 when one (ie, risk for a second man in the family to be diagnosed with PCa) and 3.7 when more than one family member were probands (Table 1). Families of more than two affected individuals (multiplex families) accounted for >10% of all families, with at least two men with PCa [16]. For cancer of kidney parenchyma, familial risk was 1.9, and in rare multiplex families, it was 5.2; for bladder cancer, the risks were 1.8 and 2.5, respectively. For rare testicular and penile cancers, the risks were high (5.2 and 7.5, respectively), and no multiplex families were found. The familial proportion was very high, 26.4%, for PCa, and this proportion was the highest among all cancers in the Swedish FCD [16]. For bladder cancer, 7.0% of patients were familial, and for kidney and the other cancers, the proportions were less.

1.2. Predisposing genes

First cancer predisposing genes were detected in the 1980s, and by 2014, a review by Rahman [17] listed over 100 genes with germline variants causing hereditary cancer. Since then, tens of novel predisposing genes have been proposed, but many lack appropriate validation in pedigrees. One unanticipated problem in the field of "high-risk" genes has been a firm belief that once a variant was found in a patient, it was causative of cancer in that patient. The discrepancy was illustrated recently in a sequencing study of germline DNA from 110 000 breast cancer patients and 53 000 healthy controls [18]. Protein-truncating variants were found in 34 well-known cancer predisposing genes, but as these variants were also found in controls, only for 12 genes the variant frequency was significantly higher in cases than in controls. When a urologist judges the association (causative role) of a predisposing gene in cancer, it is necessary for the urologist to know the variant frequency in an appropriate control population [19]. Pathological variants (PVs) are thought to be potentially disease causing in a particular cancer.

High-penetrant gene variants (PVs) currently known to predispose to urological cancers are listed in Table 2.

In addition to high-penetrance pathogenic variants, there is also a polygenic etiology for urological cancers with dozens (bladder, kidney, and testicular) to hundreds (PCa) of lower-penetrance genetic variants identified, which increase the risk of cancer (see the GWAS Catalog [ebi.ac.uk]). Using polygenic risk scores, the combination of these variants can discriminate persons with different risks for cancer. Although the cutoff point of such a liability distribution is arbitrary, the separation of higher- and lower-risk groups may have clinical relevance. For individual risk assessment, polygenic risk scores, however, might not be useful [20].

The below sections review shortly the current situation about hereditary and familial cancers in some European urology clinics, as described by residing urologists.

2. Prostate cancer

In PCa, germline mutations have been found in approximately 4–6% of men with high-risk disease and in <5% of men with low-risk localized disease, while in metastatic cancer, the incidence has been reported in 7–16%. This includes pathogenic/likely pathogenic variants ([L]PVs) predominantly seen in *BRCA2*, *HOXB13*, *BRCA1*, *CHEK2*, *PALB2*, and *ATM* genes [21]. These are DNA damage repair (DDR) and DNA mismatch repair (MMR) genes in the germline [22,23]. For men with a Gleason score of ≥8 or with intraductal or cribriform pathology, there is an association with the presence of germline (L)PVs in DDR genes.

Table 1 – Familial risks (SIR) and proportions (familial cases of all offspring) for urological cancers based on the Swedish Family-Cancer database [16][a]

Cancer	ICD-7	SIR1 proband	SIR >1 proband	Familial proportion (%)
Prostate	177	2.2	3.7	26.4
Kidney	180.0	1.9	5.2	3.8
Bladder	181.0	1.8	2.5	7.0
Testis	178	5.2	–	1.9
Penis [a]	179.0	7.5	–	0.9

CI = confidence interval; SIR = standardized incidence ratio.
[a] All SIRs were significant (lower 95% CI does not include 1.00).
[a] Data for penile cancer (squamous cell carcinoma, invasive and in situ) were obtained from the study of Hussain et al [57]. Note that the offspring case number was only 6.

Table 2 – High-penetrance pathogenic gene variants (PVs) predisposing for urological cancers[a]

Cancer	Gene	Prevalence of PV among patients with specific cancer and suspicion for a gene mutation (%)	Penetrance (%)	Type
Prostate	*BRCA2*	All genes combined approx. 6%. Most prevalent and strongest association is with *BRCA2*	?	More aggressive
	HOXB13		?	Possibly less aggressive
	BRCA1		Low	
	CHEK2		Low	
	PALB2		Low	
	ATM		Low	
Kidney	*VHL*	95	70	Clear cell
Von Hippel-Lindau	*FLCN*	4	15	Chromophobe
Birt-Hogg-Dube	*FH*	95	2–15	Papillary type 2
Hereditary leiomyomatosis and RCC	*MET*	?	2–5	Papillary type 1
Hereditary type 1 papillary RCC	*SDHB, SDHC, SDHD, TMEM127*	?	15	Various
RCC with hereditary paraganglioma	*?*	?	?	Clear cell
Chromosome 3 translocations	*PTEN*	?	?	Various
PTEN-hamartoma tumor syndrome	*TSC1, TSC2*	2–4	2–5	Various
Tuberous sclerosis complex	*BAP1*	1	6	Various
Hereditary BAP1 tumor syndrome				
Renal pelvis/ureter	*MLH1 MSH2/EPCAM*	? Strongest association with *MSH2*	1–15%	Urothelial
Lynch syndrome	*MSH6*			
	PMS2			
Bladder	*MLH1 MSH2/EPCAM*	?	1–15%	Urothelial
Lynch syndrome	*MSH6*	Strongest association with *MSH2*	Low	Early age at dx
Retinoblastoma	*PMS2*		Low	Early age at dx
Costello syndrome	*RB1*	?		
	HRAS	?		
Testis	*CHEK2?*	?	?	
Penis	None	–	–	

dx = diagnosis; RCC = renal cell carcinoma.
[a] The population prevalence of the pathogenic variants can be highly population specific. For example, the rare missense variant rs138213197[T] in *HOXB13*, encoding for p.Gly84Glu, was found in one of 66–1500 cases in six different countries in a study by Gudmundsson et al [58].

In contrast, somatic (L)PVs in DDR genes occur more frequently in around 23% of the tumor tissue of patients with metastatic castration-resistant PCa (mCRPC), mainly in *BRCA2* and *ATM* [24]. Prevalence of germline mutations in the general population and test methodology vary. As a result, international guidelines vary in their recommendations for germline and tumor genetic testing.

2.1. Screening

For men without PCa but having a relevant family history (familial PCa: three or more family members with PCa, or two or more family members with PCa diagnosed at 55 yr of age or younger, or PCa in three generations within one branch of the family, and always Gleason score $\geq$7), screening for PCa is currently recommended from the age of 50 yr. In the case of a family history of BRCA-related hereditary cancer (eg, breast, ovarian, and/or pancreatic cancer in a first- or second-degree relative), the age of initial screening is adjusted to 45 yr. If the individual BRCA2-carrier status is known to be positive, this age limit is further decreased to 40 yr [6]. The IMPACT study, which evaluates the role of targeted prostate-specific antigen (PSA) screening in men with BRCA1/2 or MMR germline (L)PVs, supports the role of annual PSA screening till the age of 70 yr in men with BRCA2, MSH2, and MSH6 germline (L)PVs [25]. In the study, magnetic resonance imaging is not a primary screening test but remains a reflex test prebiopsy in case of an individual having an increased PSA density–based risk profile.

Referral to a clinical geneticist for further genetic counseling of individuals and family members is advised in case

hereditary PCa is suspected, especially in the case of a BRCA2-related tumor. For only familial PCa, the value of counseling is still unknown.

2.2. Primary therapy and follow-up

The choice between curative treatment (surgery or radiotherapy) and active surveillance (AS) is not primarily dependent on germline status. In men with BRCA1/2 and ATM germline (L)PVs choosing AS, grade reclassification resulting in active intervention was observed more often [26]. BRCA2 carriers had a five-fold higher risk of reclassification to Gleason grade group 3 after diagnosis of Gleason grade group 1 versus noncarriers. This might be an argument for BRCA2 carriers to choose for curative treatment early on or to follow more intense monitoring during AS. Additionally, retrospective data suggest that BRCA2 patients treated with radiotherapy might have worse cause-specific survival than patients treated with surgery [27]. However, of over 400 men in the Canary Prostate Active Surveillance study, 6.6% harbored a pathogenic germline mutation, but this was not associated with adverse characteristics [28]. A bias in clinical management based on germline status may cause the difference in these observations.

Currently, in nonmetastatic disease, tumor genetic testing has limited benefit and clinical consequence, while germline testing is advised only if BRCA2 mutations are present in the family [29] but uncertain for those with only a PCa family history (Table 3).

2.3. Metastatic disease

Four biomarker-driven therapies have been approved (US Food and Drug Administration [FDA] or European Medicines Agency [EMA]) for the treatment of mCRPC, which are related to somatic DDR mutations and MMR deficiency. These are, respectively, the poly ADP-ribose polymerase (PARP) inhibitors olaparib, rucaparib, and talazoparib, and the immune checkpoint inhibitor pembrolizumab. Tumor testing of metastatic tissue is therefore needed when considering these drugs, as more than half of actionable DDR mutations are likely missed by germline testing alone [30]. The timing of testing, choice of the gene panel, and tissue of preference are still under debate. Currently, PARP inhibitors are considered only after at least one line of novel hormone agents and one line of chemotherapy [24,31].

Usually, patients with tumor-detected germline mutations are sent for germline testing, but also negative tumor testing in combination with a suspect family history might be an indication for a germline analysis, as a proportion can be missed in tumor sequencing.

2.4. Conclusion

The identification of germline and/or tumor (L)PVs can have a profound impact on the management of PCa. Increased exposure to new data will sharpen our insights and provide further guidance to clinicians.

3. Urothelial carcinoma and Lynch syndrome

Lynch syndrome (LS), previously known as hereditary nonpolyposis colorectal cancer, is a dominant familial cancer syndrome associated with an increased risk of many cancers. Hereditary urothelial cancer of the upper urinary tract (UUT) is linked to LS accounting for 20% of all urothelial cancers of the UUT, and it ranks third (5%) within LS-associated tumors. Development of LS is associated with MMR deficiency and pathogenic variants such as those of the tumor suppressor genes *MSH2*, *MSH6*, *MLH1*, and *PMS2* [32]. These MMR mutations might lead to distinct LS-associated cancer entities based on the patient's gender. In contrast to other LS-related tumors, LS-associated urothelial cancer of the UUT shows no clear gender prevalence [33]. Up to one in four LS individuals carrying the MSH2 mutation will develop urothelial cancer during their lifetime (www.plsd.eu). These defects may increase cellular proliferation and antagonize tumor suppression function. Alterations in small repetitive DNA sequences, known as microsatellite instability (MSI), are present in nearly all urological tumors associated with LS. Tumors with MSI usually show high infiltration of T cells (Th1 type) [34]. This may be a positive aspect for those patients who received chemotherapy previously, as indicated by better survival rates in patients with high MSI.

LS-associated urothelial cancer is more common in female patients and occurs at a younger age. Molecular diagnosis for LS is based on the determination of MSI and immunohistochemical detection of MMR genes. Use of immunohistochemical methodologies is recommended for the prediction of pathogenic germline variants [35]. Patients with LS-associated urothelial cancers have similar survival rates to those who are diagnosed with sporadic urothelial cancer. In detail, the 5- and 10-yr survival rates were, respectively, 81% and 68% in bladder cancer patients with pathogenic MLH1, MSH2, and MSH6 carriers, and 86% and 67%, respectively, in patients with urothelial cancer of the UUT [36].

LS-associated urothelial cancer of the UUT could be misdiagnosed frequently as sporadic if diagnostic procedures are incomplete. Interestingly, early diagnosis of LS may facilitate screening for potential associated tumors and, in consequence, reduce the cancer risk. However, introduction of a universal screening method remains challenging, but is justified in all patients with urothelial cancer of the UUT under the age of 60 yr, and those with a family history of urothelial cancer of the UUT [37,38] or positive MMR immunohistochemical findings in sporadic urothelial cancer of the UUT [39,40]. The reason is that urothelial cancer of the UUT has the highest rates of undiagnosed genetic disease in urological cancers as germline mutations in DNA MMR genes—defined as LS—are found in 9% of patients with urothelial cancer of the UUT (compared with only 1% of patients with urothelial cancer of the bladder) [41]. In case of positive germline DNA sequencing in patients with urothelial cancer of the UUT, clinical evaluation for other LS-related cancers, strict urological monitoring with follow-up, and familial genetic counseling are recommended according to the European Association of Urology

(EAU) guidelines [42]. In general, it has been assumed that cancers with higher MSI are good candidates for immunotherapy. FDA has approved pembrolizumab for all MSI-H/dMMR tumors, while EMA has approved it only for endometrial, colorectal, and some other gastrointestinal cancers. Ongoing trials evaluating the effectiveness of immune checkpoint inhibitors in LS-associated urothelial cancer are rare [43]. In addition to LS-related urothelial cancer, the familial bladder cancer risk is found to be doubled for individuals with a first-degree relative with bladder cancer [44]. An exome-sequencing study revealed multiple biologically plausible genes that might be related to familial bladder cancer. Despite heterogeneity, the identified genes clustered in common pathways such as DNA repair (*CHEK2*, *MSH2*, and *MLH1*), cellular metabolism (*ME1* and *IDH1*), and cilia biogenesis (*C2D2A*, *DNAAF4*, *DNAH5*, *IQCB1*, and *RSPH1*) [45]. Further trials are now needed to evaluate the importance of these genes being associated with familial bladder cancer.

3.1. Conclusion

Hereditary urothelial cancer of the UUT should always be suspected in case of (1) age <60 yr and a personal history of Lynch-spectrum cancer, (2) a first-degree relative aged <50 yr with Lynch-spectrum cancer, and (3) two first-degree relatives with Lynch-spectrum cancer.

Suspicion should lead to germline mutation testing and, if positive, familial genetic counseling, screening for other LS-related cancers, and close urological follow-up [42].

4. Renal cell carcinoma

Familial renal cell carcinoma (RCC) represents a minority within the spectrum of RCC, constituting only 3.8% of all cases (Table 1). Despite its low prevalence, the penetrance associated with known pathogenic gene variants is notably high, with the Von Hippel-Lindau (VHL) mutation exhibiting penetrance of 70% (Table 2). With advances in next-generation sequencing, several new hereditary syndromes have been described in the past few years [46]. Noteworthy is the familial risk (SIR), which exceeds 5 when more than one first-degree relative (or three or more affected in a family) has been diagnosed with RCC, as elucidated in Table 1.

In accordance with the EAU guidelines, hereditary RCC accounts for 5–8% of all RCC cases [42]. These guidelines delineate a dozen distinct hereditary entities associated with RCC. An intriguing characteristic of hereditary RCC is the occurrence at an earlier age, with the median age at diagnosis being 37 yr and 70% of cases diagnosed before the age of 46 yr [47]. Thus, the age of 46 yr or younger has been suggested as a cutoff to trigger consideration for genetic counseling or germline mutation testing even without clinical manifestations and a personal or family history [34].

The management of hereditary kidney cancer syndromes is related to the increase of multifocality of the disease and often necessitates repeated surgical interventions, prompting the adoption of AS until tumors reach 3 cm [48]. In contrast, nonhereditary tumors are typically addressed through immediate surgical intervention, even when diminutive in size (often 1–2 cm). The approach to hereditary RCCs leans toward individualized AS when appropriate, with multidisciplinary discussions being recommended commonly. Moreover, nephron-sparing strategies are preferred, except in cases of familial hereditary kidney cancer and succinate dehydrogenase (SDH)-related paraganglioma syndromes (Table 2) that might have a more aggressive nature and a higher chance of developing metastatic disease [42].

Within the purview of Helsinki University Hospital, which serves a population exceeding 1 million, a mere 37 patients have undergone genetic panel testing for familial RCC (unpublished data). Among these, 29 (78.4%) exhibited normal genetic profiles, while eight (21.6%) revealed known mutations (two SDHB, three FLCN, two VHL, and one BAP1), underscoring the rarity of such cases in clinical practice. Similar reports have been published by Truong et al [49] who reported 232 patients with early-onset RCC. Germline pathogenic variants or (L)PVs were identified in 41 patients (17.7%), of whom 21 (9.1%) had in an RCC-associated gene and 20 (8.6%) a non–RCC-associated gene. The RCC genes included *FH* in 12 patients, *VHL* in four, *SDHB* in two, and *BAP1*, *FLCN*, or *TSC1* in one patient [42].

Nevertheless, it is imperative to recognize that young, under 46 yr old RCC patients and those with a clear familial history may derive substantial benefits from genetic testing and counseling, given the consequential treatment implications, such as AS and nephron-sparing surgical approaches [48]. Additionally, family screening and vigilant monitoring of the affected individuals are strongly advocated. Interestingly, several hereditary RCCs are identified because these contain other noncancerous manifestations such as spontaneous pneumothorax (Birt-Hogg-Dube), hemangioblastomas (VHL), leiomyomas (HLRCC), and others.

In conclusion, hereditary RCC should be suspected if (1) several family members have RCC, (2) patient is diagnosed with RCC before the age of 46 yr, or (3) patient has several multifocal RCCs. Suspicion should lead to genetic counseling and/or germline mutation testing, regardless of the results affecting patient management (consider AS and nephron-sparing strategies) and follow-up. Discussions at multidisciplinary meetings are crucial and should be mandatory.

Table 3 – Summary of current genetic testing and treatment advice regarding locally confined PCa

Primary PCa	Act Surv possible	Perform germline testing	Perform somatic testing
Familial PCa	Yes	–?	–
Hereditary suspicion	Yes	+	–
BRCA2 carrier	High risk	(Done)	–

Act Surv = active surveillance; PCa = prostate cancer.

Table 4 – Practical clinical considerations

Germline testing	Strong advice	Consider	Do not test
Prostatic	When hereditary (BRCA2) When age <46 [a]	When familial When mCRPC	When low–risk disease
Urothelial (Lynch)	When age <60 When UUT	When colorectal cancer When endometrial cancer	When incidental bladder tumor
Renal	When age <46 When multiple When hereditary (VHL) When familial	–	–
Testicular	–	–	+

AUA = American Urological Association; mCRPC = metastatic castration-resistant prostate cancer; UUT = upper urinary tract; VHL = Von Hippel-Lindau.
[a] AUA guideline [59].

5. Testicular cancer

Testicular cancer is the most common cancer in young White men, but it represents only 1% of all adult cancers [50]. Of testicular cancers, 90–95% are germ cell tumors. The most common non–germ cell tumors are stromal Leydig cell tumors (4%) and Sertoli cell tumors (1%). Factors associated with testicular cancer are cryptorchidism, prior unilateral cancer, and family history [51–53].

5.1. *Familial risk*

Family history is a major risk factor for testicular germ cell tumors (TGCTs), and up to 50% are estimated to be hereditary; one affected family member increases the SIR to 5.2 (Table 1) [54]. However, only 1.4% of men with a TGCT report a family history, and there appears to be no major differences in age or histopathology between men with a familial or sporadic TGCT [42,43]. No high-penetrance genes have been identified. The only moderate-penetrance gene identified is the tumor suppressor gene checkpoint kinase 2 (*CHEK2*) involved in DDR [55]. Unselected men with TGCTs were four times more likely to have a CHEK2 mutation than controls and developed testicular cancer 6 yr earlier than men with wild-type CHEK2 alleles. Current evidence suggests polygenic etiology for TGCTs, and at least 22–66 susceptibility loci have been identified, but many more likely exist [54,56]. Despite the familial relative risk for TGCTs being among the highest for urological cancers, the absolute risk is modest. Yet, it is advisable to consider a family history of TGCT anamnesis and patient education as testicular self-examination may help identify TGCTs early, thereby improving outcomes [10].

A lack of high-penetrance susceptibility genes and relatively low absolute numbers of affected families will require large multi-institutional collaborative studies to attain sufficient power for identifying rare moderate-penetrance testicular cancer risk variants. This also suggests a role for polygenic risk scores [7].

6. Conclusions

The early recognition of hereditary urological cancers may influence diagnostic and therapeutic decision-making, and potentially alter the fate of patients and family members. Considering all urological cancer patients, routine inquiries about a familial cancer history should become a standard practice in clinical settings. If suspicion arises, patients can opt for two avenues: referral to genetic counseling or, increasingly in the future, undergoing genetic tests after consultation with the treating urologist, driven by the growing affordability of genetic panels (costing a few hundred euros) and the escalating demand for genetic testing, especially in the realm of PCa (BRCA2) and urothelial cancer (MSH2).

Important in the context of somatic mutation testing is that there should be a European reference database on mutation frequencies in healthy population. This would help consider whether the detected variant may be pathogenic and what advice the urologist's genetic counselor is giving the patient.

The practical clinical considerations are listed in Table 4.

A common challenge encountered in urological familial cancers is the inability of genetic tests to verify genetic defects conclusively despite evident familial clustering. Polygenic mutations, methylations, and other biological causes might explain a considerable proportion, while a smaller proportion might be due to random causes. Finding a variant of uncertain significance in which it is unclear whether this is connected to a serious health condition causes uncertainty and invites for a reanalysis at a time that more population data are available. Recommendations for such patients are a challenge, but exercising sound clinical judgment becomes imperative. Broadly, closer monitoring and, in the case of familiar RCC, nephron-sparing approaches emerge as potential suggestions.

The future relevance of genetic testing will be strongly dependent on the acquirement of large genetic data sets in combination with long-term clinical observations, and from social and technological developments. Urologists should act hand in hand with genetic counselors, oncologists, and tumor researchers in the field.

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