Genetic Testing for Prostate Cancer, Urothelial Cancer, and Kidney Cancer

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As genetic testing plays an increasingly salient role in the realm of cancer diagnosis, prognostication, and treatment, this review aims to elucidate the current landscape and future directions of genetic testing in genitourinary cancers, with a focus on prostate cancer, urothelial carcinoma, and renal cell carcinoma. With the increasing adoption of next-generation sequencing technology, the utilization and access to genetic testing in real-world settings have become critical for practicing urologists and genitourinary oncologists, especially after the approval of poly(ADP-ribose) polymerase inhibitors for prostate cancer and the utilization of immune checkpoint inhibitors. In this rapidly evolving field, this review underscores the clinical value of interpreting genetic variations and the importance of distinguishing between germline and somatic mutations, for whom testing can be prescribed, and which genes should be tested. While the current modus operandi predominantly relies on exome sequencing, we posit that the future of genetic testing in genitourinary cancers will see an expansion to encompass whole-genome sequencing, accounting for structural and regulatory variations that impact gene expression. In the upcoming era of liquid biopsies, we envisage an increase in noninvasive cancer genetic testing for the purposes of diagnosis, prognosis, treatment response, and progression monitoring, supplementing the gold-standard tissue biopsies that provide histologic information. Ultimately, thoroughly interpreting genetic testing results and the subsequent treatment implications necessitates a multidisciplinary approach. This review strives to offer urologists a comprehensive perspective on genetic testing in these prevalent urological cancers, contributing to improved diagnosis, prognosis, and treatment decision-making.

Key Words: Genetic testing, Kidney neoplasms, Urothelial carcinoma, Prostatic neoplasms
INTRODUCTION

The dropping costs and broadening role of genetic testing in guiding oncological interventions have stoked interest within urological circles [1-4]. Contemporary clinical trials increasingly use genetic test results for patient enrollment and grouping, triggering a surge in mentions of genetic testing within urological cancer treatment guidelines [5]. However, in real-world settings, the utilization of and access to genetic testing have been suboptimal [6, 7], particularly prior to the approval of poly(ADP-ribose) polymerase (PARP) inhibitors [8, 9].

For clinicians, the interpretation of genetic variants holds substantial importance [10]. This process involves the integration of diverse data points, such as statistical associations with traits, impacts on protein structure and function, and drug responses. The 5-level classification by the American College of Medical Genetics and Genomics and the 4-tier classification by the Association of Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists are employed in varying contexts [11, 12]. Clinically significant genetic alterations, known or likely to drastically affect specific gene function, are sometimes distinguished as “mutations” among all the possible “variants” [13]. In contrast, genetic alterations that do not affect gene functions are referred to as “benign” or “likely benign,” and some alterations remain “variants of unknown clinical significance.”

Genetic testing provides critical insights for cancer prognosis and treatment decision-making. For instance, BCL/ABR gene fusion serves as a diagnostic criterion and lays the foundation for targeted therapy in chronic myelogenous leukemia [14, 15]. Moreover, in solid tumors such as breast, ovarian, and prostate cancer, BRCA1 and BRCA2 test results supply valuable information for the selection of anti-cancer agents like PARP inhibitors [16, 17].

Broadly, genetic mutations are divided into germline and somatic mutations [18]. Germline mutation testing examines inherited DNA mutations, using DNA from normal cells, while somatic mutation testing detects DNA mutations originating from cancer cells [19]. In patients with solid cancer, somatic mutations are identified in tumor tissue obtained through biopsy or surgical resection. However, when direct collection is challenging or frequent somatic mutation tests are necessary, circulating cell-free tumor DNA (ctDNA) may be used [20, 21].

In this review, we scrutinize genetic testing in the context of genitourinary cancers, specifically focusing on prostate cancer, urothelial carcinoma, and renal cell carcinoma. We discuss both the germline and somatic mutation tests recommended for each cancer type, organizing our content around the target patient group for each test (who?), the target gene types (which genes?), and the testing process (how?).

PROSTATE CANCER

1. Germline Mutation Testing for Prostate Cancer (Table 1)

1) Who?

The most common histologic form of prostate cancer (PC) is prostate adenocarcinoma. The germline mutation rate of metastatic PCs (mPCs), including both metastatic hormone-sensitive PCs (mHSPCs) and metastatic castration-resistant PCs (mCRPCs), is reported to be approximately 10%-15% [3]. The most prevalent genetic mutations in these cases are BRCA2, ATM, CHEK2, BRCA1, and PALB2, in descending order. However, when tests were performed based on family history and patients’ past medical history, it was found that 17% of all PC patients, regardless of metastasis, had genetic mutations. The most prevalent genetic mutations in these cases were BRCA2, CHEK2, ATM, MUTYH, BRCA1, HOXB13, APC, MSH2, TP53, and PMS2, in descending order [22]. Families with BRCA1 or BRCA2 mutations are highly likely to have hereditary breast and ovarian cancer syndrome, which is often associated with frequent breast cancers, ovarian cancers, PCs, and exocrine pancreatic cancers [23]. For example, the probability of patients with BRCA1/2 mutations being diagnosed with breast cancer and ovarian cancer by the age of 70 could be as high as 65% and 39%, respectively. In addition, there is an increased chance of germline mutations in PC patients who had been diagnosed with male breast cancer before [5, 7, 24]. Patients with MLH1, MSH2, MSH6, PMS2, and EPCAM mutations are diagnosed with Lynch syndrome and have a higher probability of developing cancers, including colorectal
cancer, endometrial cancer, gastric cancer, ovarian cancer, upper tract urothelial cancer, cholangiocarcinoma, small bowel cancer, and glioblastoma, before their 50s [25]. This condition is also known as hereditary nonpolyposis colon cancer. Therefore, our guideline recommends germline genetic testing for PC patients, as depicted in Table 1. However, since genetic mutations can be found in patients who do not meet the criteria (such as patients with mCRPC or without a significant familial or past medical history) [18, 26, 27], this guideline should not be used as a reference to withhold genetic testing.

2) Which genes?

It is recommended to perform next-generation sequencing (NGS)-based genetic panel testing, including the genes listed below, for germline mutation analysis in patients with PC.

1) Hereditary breast and ovarian cancer syndrome-related genes [23]: BRCA1, BRCA2

2) Lynch syndrome-related genes [25]: MLH1, MSH2, MSH6, PMS2, EPCAM

3) Highly prevalent genes in the germline cells of PC patients [22, 26]: APC, ATM, ATR, BRCA1, BRCA2, BRIPI, CDH1, CDKN2A, CHEK2, FAM175A, GEN1, HOXB13, MRE11A, MSH2, MUTYH, NBN, NF1, PALB2, PMS2, RAD50, RAD51C, RAD51D, TP53

3) How?

Germline mutation testing for PC is performed using samples obtained from peripheral white blood cells, saliva, or oral mucosal cells [24]. It is recommended to conduct genetic counseling for PCs in hospital settings equipped with the necessary capabilities. Still, even in hospitals that do not provide genetic counseling services, it is recommended to conduct germline testing for PC.

2. Somatic Mutation Testing for Prostate Cancer (Table 2)

There is an increasing need to determine the tumor genomic characteristics in the treatment decision-making of mPC patients. In mPC with mutations in homologous recombination repair (HRR) genes such as BRCA1/2 (approximately 20%–25% frequency), the PARP inhibitors olaparib and rucaparib have shown improved survival benefits [28, 29]. Additionally, in mPC patients (approximately 1%–3% frequency) with defects in one or more of the 4 DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or reported as having high microsatellite instability tumors, the immune checkpoint inhibitor pembrolizumab has demonstrated disease control effects [30]. Mutations in HRR genes like BRCA1/2 and MMR genes can be detected as germline or somatic cell mutations. Therefore, in mPC patients, it is necessary to test for both germline and somatic cell mutations of these genes [1, 4, 22].

1) Who?

The timing of somatic cell mutation testing in PC patients is still a topic of debate among experts, although it is recommended during the metastatic stage of the disease. The

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Table 1

| Who? | • Personal history of primary cancer diagnosis in organs other than the prostate
|      | • Family history of PC diagnosed before the age of 60 or resulting in death in parents, siblings, or children
|      | • Family history of breast cancer, colorectal cancer, or endometrial cancer diagnosed before the age of 50 in parents, siblings, children, grandparents, grandchildren, or blood relatives, or any age diagnosis of ovarian cancer, exocrine pancreatic cancer, or high-risk/metastatic PC
|      | • Family history of 2 or more cases of breast cancer or PC in parents, siblings, children, grandparents, grandchildren, or blood relatives, excluding the individual
|      | • Presence of metastatic PC, regardless of resistance status
|      | • High-risk localized PC (N1, cT3/4, Gleason grade group 4–5, or PSA>20 ng/mL).
|      | • Intraductal/ductal or cribriform histology detected in localized PC
| Which genes? | • To identify hereditary breast/ovarian cancer syndrome (BRCA1, BRCA2)
|             | • To identify Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)
|             | • To identify other hereditary cancers (APC, ATM, BRIPI, CDH1, CDKN2A, CHEK2, FAM175A, GEN1, HOXB13, MRE11A, MUTYH, NBN, NF1, PALB2, RAD50, RAD51C, RAD51D, TP53)
|             | • Confirmation of the potential use of PARP inhibitors, such as olaparib, and platinum-based chemotherapy in mPC (BRCA1, BRCA2)
|             | • Confirmation of the potential use of pembrolizumab in mPC (MLH1, MSH2, MSH6, PMS2)

PC, prostate cancer; PSA, prostate-specific antigen.
recent Advanced PC Consensus Conference 2021 reported the results of a survey conducted among a panel of over 100 experts in the field of genetic testing, tumor molecular characterization, and selection of targeted therapies [31]. The participating experts consisted of 48% medical oncologists, 31% urologists, and 21% radiation oncologists. The survey results regarding the recommended timing for somatic cell mutation testing were as follows: mCRPC, 48%; both synchronous and asynchronous mHSPC, 39%; synchronous mHSPC only, 9%; and no testing at all, 4%. Among the experts who recommended somatic cell mutation testing in mCRPC, a majority (76%) suggested performing the test at the time of disease progression after the use of first-line new hormonal agents (NHAs; e.g., enzalutamide or abiraterone).

The strongest rationale for performing somatic cell mutation testing in current PC patients is to guide the decision-making process for drug therapies such as PARP inhibitors. Olaparib, a PARP inhibitor, can be used in mCRPC patients with disease progression after first-line NHA treatment [28]. However, the list of genes that serve as criteria for approval of NHA varies by region. In the United States, the indications include mutations in BRCA1/2 and 12 other genes, while those in Europe are limited to BRCA gene mutations only. This is based on the “PROfound: gene-by-gene analysis” study, which analyzed the survival improvement effect of olaparib on a gene-by-gene basis [28]. In Korea, as of October 2021, olaparib can be used as a treatment option for BRCA-mutated adult mCRPC patients who have experienced disease progression after NHA use. Therefore, it is recommended to perform somatic cell mutation testing at the time of confirmation of disease progression after first-line NHA administration in mCRPC patients.

Two recent clinical trials, PROpel (olaparib + abiraterone) and MAGNITUDE (niraparib + abiraterone), have demonstrated the improved progression-free survival benefit of combining PARP inhibitors with NHA as first-line therapy in mCRPC patients with BRCA mutations [32, 33]. Other ongoing clinical trials such as CASPAR (rucaparib + enzalutamide) and TALAPRO-2 (talazoparib + enzalutamide) further support the rationale for performing somatic cell mutation testing at the diagnosis of mHSPC or mCRPC [34, 35].

In Korea, NGS testing for PC is covered by insurance for stages 3 and 4, as well as for progressive, metastatic, and recurrent cancers up to 2 tests [27, 36]. Therefore, if NGS testing for germline mutations has been performed in the past for progressive, metastatic, or recurrent PC, it would be appropriate to also perform somatic cell mutation testing using NGS at the time of mCRPC after first-line NHA treatment. However, for mHSPC or mCRPC patients who have not yet undergone a response evaluation for NHAs, somatic cell mutation testing can be performed using NGS, and germline mutation testing can be performed using NGS together or using alternative methods after confirming the results of somatic cell mutation testing.

2) Which genes?

Somatic cell mutation testing in PC patients is recommended using NGS-based genetic panel testing that includes the following genes (note that there may be overlap in the gene list):

(1) HRR genes associated with indications for PARP inhibitors [28, 29, 32-35]: BRCA1, BRCA2, ATM, ATR, PALB2, FANCA, RAD51D, CHEK2, CDK12

(2) MMR genes and related tests associated with indications for pembrolizumab: MLH1, MSH2, MSH6, PMS2, microsatellite instability [37], tumor-mutational burden [38]

Table 2, Recommendations for somatic mutation testing in patients with PC

<table>
<thead>
<tr>
<th>Who?</th>
<th>• Presence of metastatic PC, regardless of resistance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which genes?</td>
<td>• Assessing the potential use of PARP inhibitors, such as olaparib, and platinum-based chemotherapy in mCRPC that has failed first-line NHA treatment (BRCA1, BRCA2)</td>
</tr>
<tr>
<td></td>
<td>• Evaluation of the potential use of pembrolizumab in mCRPC following failure of first-line NHA treatment or docetaxel (MLH1, MSH2, MSH6, PMS2, microsatellite instability, tumor-mutational burden)</td>
</tr>
<tr>
<td></td>
<td>• Frequent somatic cell mutations in mCRPC (AR, FOXA1, SPOP)</td>
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<td></td>
<td>• Indication of poor response to first-line NHA treatment in mCRPC with frequent somatic cell mutations (CDKN1B, CDKN2A, CDKN2B, FANCA, FANCL, KRAS, PIK3CA, PTEN, RB1, SMAD4, TP53)</td>
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</tbody>
</table>

PC, prostate cancer; PARP, poly(ADP-ribosel polymerase; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent.
(3) Genes that are associated with the prognosis of PC patients: AR [39], CDKN1B, CDKN2A, CDKN2B, FANCA, FANCL, FOXA1, KRAS, PIK3CA, POLE, PTEN, RB1, SMAD4, SPOP, TP53

3) How?
Somatic mutation tests could be performed with tissue or ctDNA in PC patients. Particularly, when performing ctDNA testing, it is recommended to obtain blood samples at the time of disease progression, because it is difficult to obtain a significant quantity ctDNA when patients are showing response to treatment [40].

UROTHELIAL CARCINOMA

1. Germline Mutation Test for Urothelial Cancer (Table 3)

1) Who?
Current major guidelines do not recommend testing for germline mutations in urothelial carcinoma (UC), such as bladder cancer, except in cases where Lynch syndrome is suspected due to mutations in MMR genes such as MLH1, MSH2, MSH6, PMS2 and EPCAM. For example, while UC is generally more common in the bladder than in the upper urinary tract (e.g., the renal pelvis and ureter), the incidence of upper tract UC is higher in Lynch syndrome patients (bladder cancer, 1%; upper urinary tract cancer 9%) [41, 42]. Lynch syndrome is a genetic disorder that exhibits a low diagnostic rate when it manifests as urological tumors [25]. As a clinical precaution, attention should be given to the possibility of this syndrome, especially when an upper tract UC is diagnosed, and genetic testing should be considered [43]. The following are situations in which genetic testing for Lynch syndrome is necessary.

<table>
<thead>
<tr>
<th>Who?</th>
<th>Which genes?</th>
</tr>
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<tbody>
<tr>
<td>Upper tract urothelial cancer in patients under 60 years of age</td>
<td>Diagnosis of Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)</td>
</tr>
<tr>
<td>Personal history of Lynch-spectrum tumors in organs other than the urinary tract</td>
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<tr>
<td>Parent, sibling, or child diagnosed with Lynch-spectrum tumors under the age of 50</td>
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<tr>
<td>Two or more relatives (parent, sibling, or child) diagnosed with Lynch-spectrum tumors</td>
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<tr>
<td>Lynch-spectrum tumors (lifetime risk): 20%–80% for colorectal/rectal cancer, 40%–50% for endometrial cancer, 1%–13% for gastric cancer, 1%–4% for biliary tract cancer, 1%–18% for UC (upper urinary tract and bladder combined), 1%–6% for small intestine cancer, 1%–6% for pancreatic cancer, and 1%–3% for brain tumors</td>
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</table>

3) How?
When Lynch syndrome in a UC patient is suspected, NGS gene panel testing can be conducted to investigate the MLH1, MSH2, MSH6, PMS2, and EPCAM genes [41, 42]. Germline analysis is performed using DNA extracted from peripheral blood leukocytes, saliva, or oral cells. Immunohistochemical staining of MLH1, MSH2, MSH6, and PMS2 can also be utilized to diagnose tumor tissues [46].

2. Somatic Mutation Testing for Urothelial Carcinoma (Table 4)

Although UC is ranked as the third most prevalent cancer in terms of somatic mutations, following melanoma and lung cancer [47], a significant emphasis on somatic mutation testing is surprisingly lacking in current major guidelines. This discrepancy can be attributed to the current lack of
well-established and targeted treatments based on genetic mutations specifically for UC.

1) Who?
Currently, a recommendation for genetic testing in non–muscle-invasive bladder cancer (NMIBC) within the realm of UC remains absent. Nevertheless, genomic studies utilizing NGS in NMIBC have frequently observed mutations in DDR-related genes, with ERCC2 mutations being the most prevalent. Additionally, it has been reported that ARID1A mutations are associated with failure of bacillus Calmette-Guérin therapy [48]. These findings suggest the potential inclusion of these genes in future guidelines for the management of NMIBC.

Performing genetic testing early of advanced UCs, including muscle-invasive bladder cancer (MIBC), can help prevent delays in the administration of subsequent therapies and facilitate decision-making for future potential clinical trials. Although the IMvigor 010 clinical trial, which investigated the adjuvant therapy effect of atezolizumab following radical cystectomy in MIBC, failed to demonstrate an improvement in overall survival, the observation of significant treatment efficacy of atezolizumab in patients with detectable ctDNA in their blood suggests that ctDNA can be used as a predictive marker for treatment selection [49]. Major guidelines recommend conducting somatic mutation testing in stage IVA (cT4b, any N, M0; any T, any N, M1a) or IVB (any T, any N, M1b) cases and considering somatic mutation testing in stage IIIB (cT1-T4a, N2, 3) cases [50]. In Korea, panel gene testing using NGS can be performed for advanced solid tumors corresponding to stages 3 or 4 cancer.

The U.S. Food and Drug Administration (FDA) has granted approval for the use of erdafitinib, an FGFR inhibitor, in patients with locally advanced or metastatic UC who have FGFR3 or FGFR2 gene mutations and have progressed following platinum-based chemotherapy. The approval was based on the BLC2001 clinical trial, where an objective response rate of 32.2% was reported, with an average response duration of 5.4 months [51].

2) Which genes?
Commonly observed genetic mutations in UC include CDKN2A (34%), FGFR3 (21%), PIK3CA (20%), and ERBB2 (17%) [52]. Furthermore, considering the potential for the administration of erdafitinib, which was approved by the Korean FDA in November 2022, it is essential to include the FGFR3 and FGFR2 genes when conducting somatic cell mutation genetic testing in patients with advanced UC.

(1) Genetic markers associated with the indications for FGFR inhibitors (such as erdafitinib): FGFR2, FGFR3
(2) Frequently reported mutated genes in urothelial cancer: CDKN2A, PIK3CA, ERBB2

3) How?
FGFR2 or FGFR3 gene fusion in UC tumor tissue can be identified through methods such as reverse-transcription polymerase chain reaction (RT-PCR) or NGS. In the BLC2001 clinical trial, which served as the basis for the approval of erdafitinib, RT-PCR was utilized to confirm FGFR2 or FGFR3 gene fusion or gene mutation [51]. The Korean FDA has selected the Therascreen FGFR RGQ RT-PCR kit, introduced by Qiagen Korea, as the testing method for detecting mutations in these genes.

RENAL CELL CARCINOMA

1. Germline Mutation Testing for Renal Cell Carcinoma (Table 5)

Renal cell carcinoma (RCC) can occur due to hereditary or de novo germline alterations of single genes. Although the reported prevalence of hereditary RCC is approximately 2%–8% of all types of RCC [53, 54], the actual prevalence of heredity RCC might be underestimated. Of particular note,
it has been reported that about 38% of metastatic RCC cases had germline mutations [55].

1) Who?
According to the National Comprehensive Cancer Network guidelines, American Urological Association guidelines, and European Association of Urology guidelines, physicians should consider hereditary RCC and recommend germline genetic testing and genetic counseling in the following cases of patients with RCC [56].

1. Bilateral or multiple renal tumors
2. RCC diagnosed at age ≤46 years old
3. RCC patient who has ≥1 first- or second-degree relatives* with RCC

*Close blood relatives include the patient’s first-degree (that is, parents, sibling, children) and second-degree (that is, half-siblings, aunts, uncles, nieces, nephews, grandparents, grandchildren) relatives.

Additionally, a genetic risk assessment and germline genetic testing should be recommended in patients with RCC who have the following situations:

1. An individual with a close blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene
2. An individual whose tumors have the specific histologic features, including multifocal papillary histology, hereditary leiomyomatosis and RCC (HLRCC)-associated with HLRCC, and Birt-Hogg-Dube syndrome (BHDS)-related histology (multiple chromophobe, oncocytoma, or oncocytic hybrid)

2) Which genes?
(1) Genes related to hereditary RCC syndromes*: VHL, MET, FLCN, TSC1, TSC2, FH, BAP1, SDHA, SDHB, SDHC, SDHD
(2) Cowden syndrome, MITF cancer syndrome, CHECK2-associated syndrome, and hyperparathyroid jaw tumor syndrome-related genes [57]: PTEN, MITF, CHECK2, CDC7
*Von Hippel-Lindau, hereditary papillary renal carcinoma, BHDS, tuberous sclerosis complex, HLRCC, BAP1 tumor predisposition syndrome, hereditary paraganglioma/pheochromocytoma syndrome.

3) How?
In patients with RCC who are at risk of germline mutations, NGS-based gene panel testing should be recommended for a germline genetic test using genomic DNA obtained from body fluids, such as blood or saliva.

2. Somatic Mutation Testing for Renal Cell Carcinoma (Table 6)

1) Who?
Many of the characteristics of somatic mutations in RCC have been revealed through the TCGA (The Cancer Genome Atlas) project [58], and key mutation profiles are different

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**Table 5. Recommendations for germline mutation testing in patients with RCC**

<table>
<thead>
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<th>Who?</th>
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<tr>
<td>Bilateral or multiple renal masses</td>
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<tr>
<td>Diagnosed at age ≤46 years old</td>
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<tr>
<td>≥1 first- or second-degree relatives* with RCC</td>
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<table>
<thead>
<tr>
<th>Which genes?</th>
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<tbody>
<tr>
<td>VHL (Von Hippel-Lindau syndrome)</td>
<td></td>
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<tr>
<td>MET (hereditary papillary RCC)</td>
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</tr>
<tr>
<td>FLCN (Birt-Hogg-Dube Syndrome)</td>
<td></td>
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<tr>
<td>TSC1, TSC2 (tuberous sclerosis complex)</td>
<td></td>
</tr>
<tr>
<td>FH (hereditary leiomyomatosis renal cell carcinoma)</td>
<td></td>
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<tr>
<td>BAP1 (BAP1 tumor predisposition syndrome)</td>
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<tr>
<td>SDHA, SDHB, SDHC, SDHD (hereditary paraganglioma/pheochromocytoma syndrome)</td>
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<tr>
<td>PTEN (Cowden syndrome)</td>
<td></td>
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<tr>
<td>MITF (MITF cancer syndrome)</td>
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<tr>
<td>CHEK2 (CHEK2-associated syndrome)</td>
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<td>CDC7 (hyperparathyroid jaw tumor syndrome)</td>
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</tbody>
</table>

RCC, renal cell carcinoma.

*Close blood relatives include the patient’s first-degree (that is, parents, sibling, children) and second-degree (that is, half-siblings, aunts, uncles, nieces, nephews, grandparents, grandchildren) relatives.
according to the histologic subtypes of RCC.

1) Clear cell type

The most common somatic mutations of clear cell renal cell carcinoma (ccRCC), which is the most common histologic subtype of RCC (about 80% of total RCCs), are VHL (60%–70%), PBRM1 (40%), SETD2 (15%) and BAP1 (10%), and these genes are all located in the chromosome 3p21 region and are adjacent to each other [58]. Although VHL gene mutation has been regarded as the key factor for angiogenesis and proliferation of tumor cells in ccRCC, there is no clear evidence that VHL mutation is associated with the prognosis of patients or responsiveness to vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) [59]. However, recent NGS data from the CheckMate-009, -010, and -025 studies revealed that patients with advanced ccRCC who had PBRM1 mutations showed better therapeutic responses and prolonged survival after treatment with immune checkpoint blockades, such as anti-PD1 inhibitor use [60, 61]. In contrast, mutations in the BAP1 and SETD2 genes, which encode histone and chromatin remodeling factors, as well as mutations of TP53 and CDKN2A genes are associated with a poor prognosis [59, 62]. Additionally, patients with ARID1A mutations who were treated with a combination with atezolizumab (an anti-PD1 inhibitor) and bevacizumab showed better progression-free survival than those treated with sunitinib [63]. According to the presence of DDR genes (CHEK2, ATM, MSH2, and MSH6), while there was no difference in responsiveness in the TKI group, patients who had DDR gene mutations showed significantly better survival outcomes than those without DDR gene mutations in the immune checkpoint inhibitor group [64].

2) Papillary type

Papillary RCC is the second most common histologic subtype, comprising 10%–15% of RCC, and mutations of the VHL gene have been found in about 1% of patients with papillary RCC [58]. Instead, mutations in the MET (8%) and CDKN2A (5%–18%) genes are common in papillary RCC. Interestingly, MET signaling pathway inhibitors, including crizotinib, savolitinib, and foretinib, showed significant therapeutic effects in phase 2 clinical trials; therefore, the presence of MET gene mutations can be a crucial factor in determining treatment options for patients with papillary RCC [59]. Patients with papillary RCC who had CDKN2A mutations showed a poor prognosis, like ccRCC patients with CDKN2A mutations.

3) Chromophobe type

Chromophobe RCC is found in about 5% of RCC cases, and in contrast to ccRCC or papillary RCC, the most common mutations in chromophobe RCC are in the TP53 (31%) and PTEN (8%) genes. In particular, it was reported that patients with chromophobe RCC who had PTEN mutations showed a poor prognosis [58, 59].

2) Which genes?

When designing an NGS gene panel for somatic mutation testing in RCC, the essential genes for the NGS panel of solid tumors recommended by Health Insurance Review and Assessment Service and genetic differences depending on the histological subtype should be considered, and the mutation frequency, prognostic significance and association with treatment outcomes should also be considered. In particular, we recommend testing genes that are commonly detected in each histologic subtype of RCC and have been reported to exhibit prognostic significance, such as therapeutic responsiveness: VHL, PBRM1, SETD2, BAP1, TP53, CDKN2A, ARID1A, DNA damage repair genes (CHEK2, ATM, MSH2, MSH6), MET, PTEN

3) How?

In patients with RCC, an NGS-based gene panel test should be recommended for a somatic mutation test using genomic DNA obtained from primary or metastatic tissues.

Table 6. Recommendations for somatic mutation testing in patients with renal cell carcinoma

<table>
<thead>
<tr>
<th>Who?</th>
<th>Stage 3 (advanced) or stage 4 (metastatic) renal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which genes?</td>
<td>Predictive markers of immune checkpoint inhibitor responsiveness, such as anti-PD1 inhibitors (PBRM1, ARID1A, MSH2, MSH6, CHEK2, ATM)</td>
</tr>
</tbody>
</table>

PD-1, programmed cell death protein 1; TKI, tyrosine kinase inhibitor.
CONCLUSION

We reviewed the applications of genetic testing in urological cancers in terms of germline and somatic mutations. Germline mutation testing provides invaluable risk assessment data, detailing potential types and ages of cancer onset for patients and their immediate relatives. Somatic mutation testing, in contrast, facilitates the anticipation of potential drug resistance in the metastatic phase and aids in the exploration of alternative therapeutic strategies, such as immune checkpoint inhibitors and PARP inhibitors. It is projected that genetic testing will continue to grow in importance, not only in metastatic cancer cases but also in locally advanced cancers where it can inform the selection of neo-adjuvant and adjuvant therapies [65-67].

Currently, NGS-based gene panel tests primarily target exon regions, successfully detecting single-nucleotide variations (SNVs) and small indels that directly influence protein production. However, the detection of SNVs or small indels in intron regions, which indirectly impact gene expression, and large, complex structural variations remain challenging [10, 68-70]. It thus suggests the potential future adoption of whole-genome sequencing, capable of identifying structural and regulatory mutations inclusive of intron regions [71, 72]. Continued research and development in this area are imperative.

ctDNA tests, utilizing blood and urine samples, are quickly advancing as noninvasive cancer somatic gene mutation testing tools [20, 21, 49]. We anticipate an uptick in the utilization of these tests not only for diagnostic and prognostic purposes, but also for monitoring therapeutic response and disease progression [73-78].

Interpreting genetic test results requires considering numerous facets, including the possibility of false positives and negatives, and the implications of secondary findings unrelated to the initial testing purpose [79-81]. The application of these results necessitates comprehensive patient and familial counseling and a careful examination of potential clinical trial enrollment within and outside the institution. Therefore, a multidisciplinary approach is warranted, encompassing not only urologists but also hematologists, pathologists, laboratory medicine physicians, and genetic counselors involved in patient care [5, 82]. This holistic approach promises to propel the field of urological oncology forward, improving patient outcomes through personalized care strategies.

NOTES

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