REVIEW ARTICLE

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*, *BRIP1*, *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

Table 1, Recommendations for germline mutation testing in patients with PC

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*, *BRIP1*, *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 demon-strated 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

Who?	• Presence of metastatic PC, regardless of resistance status
Which genes?	• 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*)
	• 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*)
	• Frequent somatic cell mutations in mCRPC (*AR*, *FOXA1*, *SPOP*)
	• 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*)

PC, prostate cancer; PARP, poly(ADP-ribose) 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.

(1) Upper tract UC in patients under 60 years of age
(2) Patients with Lynch-spectrum tumors*, or those who have siblings, parents, or children under 50 years of age with Lynch-spectrum tumors

*Lynch-spectrum tumors [44]: when diagnosed with Lynch syndrome, the lifetime risk of cancer varies by organ: 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, among others.

2) Which genes?

Lynch-related genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* gene [45]

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

Table 3. Recommendations for germline mutation testing in patients with urothelial carcinoma

Who?	• Upper tract urothelial cancer in patients under 60 years of age
	• Personal history of Lynch-spectrum tumors in organs other than the urinary tract
	• Parent, sibling, or child diagnosed with Lynch-spectrum tumors under the age of 50
	• Two or more relatives (parent, sibling, or child) diagnosed with Lynch-spectrum tumors
	• 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 urothelial cancer (upper tract urothelial cancer and bladder cancer), 1%–6% for small intestine cancer, 1%–6% for pancreatic cancer, and 1%–3% for brain tumors
Which genes?	• Diagnosis of Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*)

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,

Table 4. Recommendations for somatic mutation testing in patients with urothelial carcinoma

Who?	• Stage III B or IV metastatic urothelial cancer
Which genes?	• Confirmation of the potential use of FGFR inhibitors, such as erdafitinib (*FGFR2*, *FGFR3*)
	• Genes frequently reported with mutations in urothelial cancer (*CDKN2A*, *PIK3CA*, *ERBB2*)

FGFR, fibroblast growth factor receptor.

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[a] 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

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

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

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 3p.21 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

Who?	• Stage 3 (advanced) or stage 4 (metastatic) renal cell carcinoma
Which genes?	• Predictive markers of immune checkpoint inhibitor responsiveness, such as anti-PD1 inhibitors (*PBRM1*, *ARID1A*, *MSH2*, *MSH6*, *CHEK2*, *ATM*)
	• Predictive markers of MET gene TKIs, such as crizotinib and savolitinib (*MET*)
	• Poor therapeutic responsiveness markers for TKIs or immune checkpoint inhibitors (*BAP1*, *SETD2*, *PTEN*, *TP53*, *CDKN2A*)

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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REFERENCES

1. Rebbeck TR, Burns-White K, Chan AT, Emmons K, Freedman M, Hunter DJ, et al. Precision prevention and early detection of cancer: fundamental principles. Cancer Discov 2018;8:803-11.
2. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-25.
3. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; 375:443-53.
4. Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 2017;318:825-35.
5. Russo J, Giri VN. Germline testing and genetic counselling in prostate cancer. Nat Rev Urol 2022;19:331-43.
6. Kurian AW, Abrahamse P, Furgal A, Ward KC, Hamilton AS, Hodan R, et al. Germline genetic testing after cancer diagnosis. JAMA 2023;330:43-51.

7. So MK, Ahn HK, Huh J, Kim KH. Germline pathogenic variants in unselected Korean men with prostate cancer. Investig Clin Urol 2022;63:294-300.

8. Shore N, Ionescu-Ittu R, Yang L, Laliberte F, Mahendran M, Lejeune D, et al. Real-world genetic testing patterns in metastatic castration-resistant prostate cancer. Future Oncol 2021;17:2907-21.

9. Leith A, Ribbands A, Kim J, Last M, Barlow S, Yang L, et al. Real-world homologous recombination repair mutation testing in metastatic castration-resistant prostate cancer in the USA, Europe and Japan. Future Oncol 2022;18:937-51.

10. Marian AJ. Clinical interpretation and management of genetic variants. JACC Basic Transl Sci 2020;5:1029-42.

11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17:405-24.

12. Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn 2017;19:4-23.

13. Duzkale H, Shen J, McLaughlin H, Alfares A, Kelly MA, Pugh TJ, et al. A systematic approach to assessing the clinical significance of genetic variants. Clin Genet 2013;84:453-63.

14. Westbrook CA, Hooberman AL, Spino C, Dodge RK, Larson RA, Davey F, et al. Clinical significance of the BCR-ABL fusion gene in adult acute lymphoblastic leukemia: a Cancer and Leukemia Group B Study (8762). Blood 1992;80:2983-90.

15. O'Dwyer ME, Druker BJ. STI571: an inhibitor of the BCR-ABL tyrosine kinase for the treatment of chronic myelogenous leukaemia. Lancet Oncol 2000;1:207-11.

16. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244-50.

17. Underhill C, Toulmonde M, Bonnefoi H. A review of PARP inhibitors: from bench to bedside. Ann Oncol 2011;22:268-79.

18. Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and somatic mutations in prostate cancer for the clinician. J Natl Compr Canc Netw 2019;17:515-21.

19. Gomella PT, Mark JR, Giri VN, Kelly WK, Gomella LG. Guidelines on germline testing for urologic tumor syndromes. Eur Urol Focus 2022;8:670-3.

20. Taavitsainen S, Annala M, Ledet E, Beja K, Miller PJ, Moses M, et al. Evaluation of commercial circulating tumor DNA test in metastatic prostate cancer. JCO Precis Oncol 2019;3: PO.19.00014.

21. Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol 2022;33:750-68.

22. Nicolosi P, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019;5:523-8.

23. Yoshida R. Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. Breast Cancer 2021;28:1167-80.

24. Giri VN, Hegarty SE, Hyatt C, O'Leary E, Garcia J, Knudsen KE, et al. Germline genetic testing for inherited prostate cancer in practice: implications for genetic testing, precision therapy, and cascade testing. Prostate 2019;79:333-9.

25. Idos G, Valle L. Lynch syndrome. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. GeneReviews(®). Seattle (WA): University of Washington; 1993.

26. Greenberg SE, Hunt TC, Ambrose JP, Lowrance WT, Dechet CB, O'Neil BB, et al. Clinical germline testing results of men with prostate cancer: patient-level factors and implications of NCCN guideline expansion. JCO Precis Oncol 2021;5: PO.20.00432.

27. Kang M, Cho E, Jang J, Lee J, Jeon Y, Jeong BC, et al. Genomic analysis of Korean patients with advanced prostate cancer by use of a comprehensive next-generation sequencing panel and low-coverage, whole-genome sequencing. Investig Clin Urol 2019;60:227-34.

28. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-102.

29. Fizazi K, Piulats JM, Reaume MN, Ostler P, McDermott R, Gingerich JR, et al. Rucaparib or physician's choice in metastatic prostate cancer. N Engl J Med 2023;388:719-32.

30. Maio M, Ascierto PA, Manzyuk L, Motola-Kuba D, Penel N, Cassier PA, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022; 33:929-38.

31. Gillessen S, Armstrong A, Attard G, Beer TM, Beltran H, Bjartell A, et al. Management of patients with advanced prostate cancer: report from the Advanced Prostate Cancer Consensus Conference 2021. Eur Urol 2022;82:115-41.

32. Saad F, Armstrong AJ, Thiery-Vuillemin A, Oya M, Loredo E, Procopio G, et al. PROpel: phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-

line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2022; 40(6_suppl):11.

33. Chi KN, Rathkopf D, Smith MR, Efstathiou E, Attard G, Olmos D, et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol 2023;41: 3339-51.

34. Rao A, Ryan CJ, VanderWeele DJ, Heller G, Lewis LD, Watt C, et al. CASPAR (Alliance A031902): a randomized, phase III trial of enzalutamide (ENZ) with rucaparib (RUCA)/ placebo (PBO) as a novel therapy in first-line metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2021;39(6_suppl):TPS181.

35. Agarwal N, Azad A, Carles J, Fay AP, Matsubara N, Heinrich D, et al. TALAPRO-2: phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2023;41(6_suppl):LBA17.

36. Suh J, Jeong CW, Choi S, Ku JH, Kim HH, Kim KS, et al. Targeted next-generation sequencing for locally advanced prostate cancer in the Korean population. Investig Clin Urol 2020;61:127-35.

37. Maio M, Ascierto PA, Manzyuk L, Motola-Kuba D, Penel N, Cassier PA, et al. Pembrolizumab in microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) cancers: Updated analysis from phase 2 KEYNOTE-158 study. J Clin Oncol 2021;39(15_suppl):2565.

38. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-65.

39. Morova T, McNeill DR, Lallous N, Gönen M, Dalal K, Wilson DM, et al. Androgen receptor-binding sites are highly mutated in prostate cancer. Nat Commun 2020;11:832.

40. Vandekerkhove G, Struss WJ, Annala M, Kallio HML, Khalaf D, Warner EW, et al. Circulating tumor DNA abundance and potential utility in de novo metastatic prostate cancer. Eur Urol 2019;75:667-75.

41. Ju JY, Mills AM, Mahadevan MS, Fan J, Culp SH, Thomas MH, et al. Universal Lynch syndrome screening should be performed in all upper tract urothelial carcinomas. Am J Surg Pathol 2018;42:1549-55.

42. Kim MH, Kim DW, Lee HS, Bang SK, Seo SH, Park KU, et al. Universal screening for Lynch syndrome compared with pedigree-based screening: 10-year experience in a tertiary hospital. Cancer Res Treat 2023;55:179-88.

43. Harper HL, McKenney JK, Heald B, Stephenson A, Campbell SC, Plesec T, et al. Upper tract urothelial carcinomas: frequency of association with mismatch repair protein loss and lynch syndrome. Modern Pathology 2017;30:146-56.

44. Watson P, Riley B. The tumor spectrum in the Lynch syndrome. Fam Cancer 2005;4:245-8.

45. Ligtenberg MJ, Kuiper RP, Geurts van Kessel A, Hoogerbrugge N. EPCAM deletion carriers constitute a unique subgroup of Lynch syndrome patients. Fam Cancer 2013;12: 169-74.

46. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26: 5783-8.

47. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

48. Pietzak EJ, Bagrodia A, Cha EK, Drill EN, Iyer G, Isharwal S, et al. Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. Eur Urol 2017;72:952-9.

49. Powles T, Assaf ZJ, Davarpanah N, Banchereau R, Szabados BE, Yuen KC, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature 2021;595:432-7.

50. Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, et al. NCCN Guidelines(R) insights: bladder cancer, version 2.2022. J Natl Compr Canc Netw 2022;20:866-78.

51. Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019;381:338-48.

52. Ross JS, Wang K, Khaira D, Ali SM, Fisher HA, Mian B, et al. Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations. Cancer 2016;122:702-11.

53. Adeniran AJ, Shuch B, Humphrey PA. Hereditary renal cell carcinoma syndromes: clinical, pathologic, and genetic features. Am J Surg Pathol 2015;39:e1-18.

54. Bratslavsky G, Mendhiratta N, Daneshvar M, Brugarolas J, Ball MW, Metwalli A, et al. Genetic risk assessment for hereditary renal cell carcinoma: clinical consensus statement. Cancer 2021;127:3957-66.

55. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al. Familial risk and heritability of cancer among twins in nordic countries. JAMA 2016;315:68-76.

56. National Comprehensive Cancer Network. Kidney cancer (version 3.2022) [Internet]. Fort Wathington (PA): National Comprehensive Cancer Network; 2022 [cited 2022 Jul 1]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.

57. Lui ST, Shuch B. Genetic testing in kidney cancer patients: who, when, and how? Eur Urol Focus 2019;5:973-6.

58. Ricketts CJ, De Cubas AA, Fan H, Smith CC, Lang M,

Reznik E, et al. The cancer genome atlas comprehensive molecular characterization of renal cell carcinoma. Cell Rep 2018;23:3698.

59. Light A, Ahmed A, Dasgupta P, Elhage O. The genetic landscapes of urological cancers and their clinical implications in the era of high-throughput genome analysis. BJU Int 2020;126:26-54.

60. Miao D, Margolis CA, Gao W, Voss MH, Li W, Martini DJ, et al. Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. Science 2018;359: 801-6.

61. Braun DA, Hou Y, Bakouny Z, Ficial M, Sant' Angelo M, Forman J, et al. Interplay of somatic alterations and immune infiltration modulates response to PD-1 blockade in advanced clear cell renal cell carcinoma. Nat Med 2020;26:909-18.

62. Voss MH, Reising A, Cheng Y, Patel P, Marker M, Kuo F, et al. Genomically annotated risk model for advanced renal-cell carcinoma: a retrospective cohort study. Lancet Oncol 2018;19:1688-98.

63. Motzer RJ, Banchereau R, Hamidi H, Powles T, McDermott D, Atkins MB, et al. Molecular subsets in renal cancer determine outcome to checkpoint and angiogenesis blockade. Cancer Cell 2020;38:803-17.e4.

64. Ged Y, Chaim JL, DiNatale RG, Knezevic A, Kotecha RR, Carlo MI, et al. DNA damage repair pathway alterations in metastatic clear cell renal cell carcinoma and implications on systemic therapy. J Immunother Cancer 2020;8:e000230.

65. Barone B, Calogero A, Scafuri L, Ferro M, Lucarelli G, Di Zazzo E, et al. Immune checkpoint inhibitors as a neoadjuvant/adjuvant treatment of muscle-invasive bladder cancer: a systematic review. Cancers 2022;14:2545.

66. Marandino L, Raggi D, Necchi A, Capitanio U. Neoadjuvant treatment in renal cell carcinoma: transforming challenges into opportunities. Eur Urol 2022;81:574-5.

67. Tewari AK, Cheung ATM, Crowdis J, Conway JR, Camp SY, Wankowicz SA, et al. Molecular features of exceptional response to neoadjuvant anti-androgen therapy in high-risk localized prostate cancer. Cell Rep 2021;36:109665.

68. Huddleston J, Chaisson MJP, Steinberg KM, Warren W, Hoekzema K, Gordon D, et al. Discovery and genotyping of structural variation from long-read haploid genome sequence data. Genome Res 2017;27:677-85.

69. Liu S, Huang S, Rao J, Ye W; Genome Denmark ConsortiumII; Krogh A, et al. Discovery, genotyping and characterization of structural variation and novel sequence at single nucleotide resolution from de novo genome assemblies on a population scale. Gigascience 2015;4:64.

70. Alkan C, Coe BP, Eichler EE. Genome structural variation discovery and genotyping. Nat Rev Genet 2011;12:363-76.

71. Souche E, Beltran S, Brosens E, Belmont JW, Fossum M, Riess O, et al. Recommendations for whole genome sequencing in diagnostics for rare diseases. Eur J Hum Genet 2022;30:1017-21.

72. Zhao EY, Jones M, Jones SJM. Whole-genome sequencing in cancer. Cold Spring Harb Perspect Med 2019;9:a034579.

73. Lau E, McCoy P, Reeves F, Chow K, Clarkson M, Kwan EM, et al. Detection of ctDNA in plasma of patients with clinically localised prostate cancer is associated with rapid disease progression. Genome Med 2020;12:72.

74. Goodall J, Assaf ZJ, Shi Z, Seed G, Zhang L, Lauffer B, et al. Circulating tumor DNA (ctDNA) dynamics associate with treatment response and radiological progression-free survival (rPFS): analyses from a randomized phase II trial in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2020;38(15_suppl):5508.

75. Kim YJ, Kang Y, Kim JS, Sung HH, Jeon HG, Jeong BC, et al. Potential of circulating tumor DNA as a predictor of therapeutic responses to immune checkpoint blockades in metastatic renal cell carcinoma. Sci Rep 2021;11:5600.

76. Basu A, Kollipara R, Sudhaman S, Mahmood T, Pajak N, Carson C, et al. Longitudinal detection of circulating tumor DNA in patients with advanced renal cell carcinoma. Journal of Clinical Oncology 2023;41(6_suppl):715.

77. Christensen E, Birkenkamp-Demtröder K, Sethi H, Shchegrova S, Salari R, Nordentoft I, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. J Clin Oncol 2019;37: 1547-57.

78. Vandekerkhove G, Lavoie JM, Annala M, Murtha AJ, Sundahl N, Walz S, et al. Plasma ctDNA is a tumor tissue surrogate and enables clinical-genomic stratification of metastatic bladder cancer. Nat Commun 2021;12:184.

79. Tandy-Connor S, Guiltinan J, Krempely K, LaDuca H, Reineke P, Gutierrez S, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 2018;20:1515-21.

80. Maani N, Panabaker K, McCuaig JM, Buckley K, Semotiuk K, Farncombe KM, et al. Incidental findings from cancer next generation sequencing panels. NPJ Genom Med 2021; 6:63.

81. Pujol P, Vande Perre P, Faivre L, Sanlaville D, Corsini C, Baertschi B, et al. Guidelines for reporting secondary findings of genome sequencing in cancer genes: the SFMPP recommendations. Eur J Hum Genet 2018;26:1732-42.

82. Shore ND, Morgans AK, El-Haddad G, Srinivas S, Abramowitz M. Addressing challenges and controversies in the management of prostate cancer with multidisciplinary teams. Target Oncol 2022;17:709-25.