

## Evolving Role of Genomics in Genitourinary Neoplasms

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The aim of this article is to review the current role of genomic testing in the risk, prognosis, and treatment of genitourinary malignancies. The authors selected guidelines, publications, and abstracts relevant to the current and emerging role of genomics in genitourinary cancers. The risk of developing genitourinary cancer can be stratified based on genomic data. Prostate cancer has the strongest degree of heritability, with *BRCA1/2* and *HOXB13* mutations playing a role in familial disease. Genomic data is on the verge of informing treatment decisions across genitourinary cancers. mCRPC has diverse genomic alterations that represent potential therapeutic targets, including alterations in the AR pathway, DNA damage and repair pathways, cell cycle pathways, PI3K pathway, and Wnt signaling. Genomic alterations in clear cell renal cell carcinoma can inform prognosis and mutations in mTOR pathways predict response to mTOR inhibitors. Urothelial carcinoma can be classified into different subtypes based on gene expression profiling, which provides prognostic information and predicts response to chemotherapy and immunotherapy. Specific mutations have been identified that predict response to therapy including *ERCC2* mutations and cisplatin, DNA damage and repair mutations and checkpoint inhibitors, and *FGFR3* mutations and FGFR tyrosine kinase inhibitors such as erdafitinib. **Conclusion.** Genitourinary malignancies have not felt the impact of genomic data as greatly as other cancer types. The majority of benefit lies in identifying patients at high risk of genitourinary cancer. Fortunately, breakthroughs are on the horizon that will result in a greater incorporation of genomic information into treatment decisions for patients with genitourinary cancer.

### Introduction

Genomic testing has altered the practice of oncology, informing multiple facets of the care of patients with a variety of neoplasms. The myriad of publications from the Human Genome project has led to a paradigm shift and changes in our ability to correlate genetic information with biologic behavior. Rapid developments in technology resulting in more cost effective and faster sequencing of genetic information, led to the swift, albeit

still evolving integration of this information into clinical practice. Genetic information may help identify populations at a high risk of genitourinary malignancies and can increasingly inform treatment decisions.

In this review, we aim to provide an overview of the role of genomic testing in the care of patients with genitourinary malignancies, focusing on prostate, kidney, and urothelial cancers, and touch on some of the emerging applications of genomics that may evolve into standards of care.

## Prostate Cancer

### *Genomics Inform Risk*

Prostate cancer represents one of the most heritable forms of malignancy. The Nordic Twin Study of Cancer showed an increase in the relative risk of developing prostate cancer of up to 5.69 times and 1.7 times for monozygotic and dizygotic twins respectively (1, 2). Men with a positive family history of prostate cancer in a first degree relative are at higher risk of prostate cancer, which further increases if more than one first degree relative is affected (3). Mutations in the genes homeobox B13 (*HOXB13*) and breast cancer susceptibility types 1 and 2 (*BRCA1/2*) have been associated with familial clusters of prostate cancer. *HOXB13* is a tumor suppressor gene that encodes for a DNA-binding domain. The mutation G48E in *HOXB13* was associated with familial prostate cancer in 2012 (4) and has subsequently been shown to confer an approximately 4.5 fold increased risk in the development of prostate cancer for carriers of the mutation (5). *BRCA1/2* encode for DNA repair machinery and have been implicated in the hereditary breast and ovarian cancer (HBOC) syndrome. Men carrying mutations in *BRCA1* or *BRCA2* have an increased risk of developing prostate cancer by up to 3.8 fold and 8.6 fold respectively (6). In addition, *BRCA2* mutations have been associated with an earlier onset of prostate cancer (7, 8) and both *BRCA1* and *BRCA2* mutations with more aggressive clinicopathologic disease (9, 10). The DNA mismatch repair proteins encoded by the genes *MSH2*, *MLH1*, and *MSH6*, have also been associated with an increased risk of prostate cancer in the Danish HNPCC registry (11). However, these genes account for a small proportion of the heritable risk. Genome wide association studies have shown nearly 170 single nucleotide polymorphisms (SNPs) that are associated with an increased risk of prostate

cancer (12). No individual SNP variant carries substantial risk on its own to be of clinical utility.

Men with a known family history of Lynch syndrome or mutation in *HOXB13* or *BRCA1/2* should be informed of the risks associated with these mutations and the utility of germline testing if they do not have prostate cancer. This may provide information relevant to the risk and benefit counseling regarding the utility of prostate specific antigen (PSA) screening. A family history suggestive of the HBOC syndrome should also prompt a discussion regarding the utility of germline testing for the presence of *BRCA1/2*, preferably with a genetic counselor when available (13).

### *Clinical Decision Making*

Genomic testing can help inform prognosis and treatment in patients with an established diagnosis of prostate cancer. The utility of genomic testing has been primarily shown in the metastatic castrate-resistant prostate cancer (mCRPC). mCRPC harbors a multitude of genomic variations. Mutations affecting the androgen receptor pathway, DNA mismatch repair machinery, cell cycle pathway, phosphatidylinositol-3-kinase (PI3K) pathway, and Wnt signaling have been identified (14). Therapeutic agents targeting each of these pathways have been developed or are in development and several are being tested in prostate cancer.

Mutations in the androgen receptor (AR) pathway are present frequently in prostate cancer, occurring in over 70% of mCRPC cases in a series of 150 patients (14), confirming the importance of the AR pathway in the pathogenesis of prostate cancer. This dependence on AR signaling, even in the advanced castrate-resistant state, establishes a biologic rationale for the efficacy of next generation anti-androgens such as abiraterone acetate and enzalutamide. Ge-

nomic alterations in the AR pathway can lead to resistance to these agents. AR-V7 is a splice variant of the androgen receptor that leads to resistance to abiraterone and enzalutamide and develops in nearly a third of men treated with these agents (15). Recently presented data from the prospective, multicenter PROPHECY trial showed that patients with AR-V7 positivity determined by circulating tumor cells were unlikely to respond to abiraterone or enzalutamide and had shortened progression free survival and overall survival (16). AR-V7 does not confer resistance to non-AR targeted therapies and there is evidence that treatment with docetaxel may eliminate AR-V7 clones (17). Whether this can re-sensitize a patient to AR-targeted therapy remains in question.

Mutations in DNA-repair genes have been identified as an important and potentially under-identified contributor to prostate cancer. In mCRPC, mutations in DNA repair may be present in up to 22.7% of patients (14). More importantly, germline mutations in these genes are fairly common and under-identified. In a population of 692 men with metastatic prostate cancer, germline mutations in the DNA-repair genes *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, *RAD51D*, and *PALB2* were identified in 11.8% of patients (18). Current guidelines recommend testing men for the presence of *BRCA1/2* mutations in men with prostate cancer with a Gleason score of 7 or greater and one of the following: close relative with ovarian or breast cancer diagnosed at age 50 or younger; or at least two relatives with breast, ovarian, or prostate cancer (Gleason 7 or greater) at any age (13). However, recent data suggests that as many as 40% of men with prostate cancer and germline mutations do not meet criteria for testing under the current guidelines (19), which likely contributes to the under-recognition of these germline abnormalities. In addition, guidelines only focus on the testing for *BRCA1/2* and do not include recom-

mendation regarding broad testing for the other potential germline mutations. Several classes of therapeutics have potential activity in patients with defective DNA repair genes, including immunotherapy, PARP inhibitors, and platinum chemotherapy. Defects leading to microsatellite instability represent a prostate cancer population that has a much greater chance of response to immune checkpoint inhibitors but are found in <2.5% of patients (20). Patients with Lynch syndrome associated prostate cancers have a higher likelihood of microsatellite instability (11). Platinum-based chemotherapy has also been associated with improved responses in patients with DNA repair defects in the *BRCA2* gene (21). The role of PARP inhibitors in the treatment of prostate cancer is an area of active research. Early data showed that in patients with known defects in DNA repair machinery who had progressed on standard therapies, olaparib elicited an overall response rate of 33% with response defined as either PSA decline of 50% or greater, radiographic response by RECIST 1.1, or a reduction in volume of circulating tumor cells (22). Multiple phase III trials investigating the role of PARP inhibitors in mCRPC are ongoing, both in selected and unselected patient populations, as well as single agent and combination therapy.

PI3K pathway mutations may be present in almost 50% of mCRPC (14). The mutated genes in this pathway included *PTEN*, *PIK3CA*, *AKT1*, and *PIK3CB*. The use of PI3K inhibitors has been studied in unselected patients with mCRPC. Buparlisip, a pan-class I PI3K inhibitor, did not yield PSA responses in men with mCRPC who had progressed on docetaxel and/or enzalutamide in a single arm phase II trial (23). In a small phase I trial, a novel inhibitor of PI3K $\beta$  showed some evidence of activity in mCRPC patients whose tumors harbored *PI3KCB* abnormalities (24). This is an emerging area of research.

## Summary

Genomic alterations have become increasingly important to our understanding of the biology of prostate cancer (Table 1). Genetics clearly play a role in an individual's risk of developing prostate cancer, with connections between mutations in *HOXB13* and *BRCA1/2* to familial clusters of prostate cancer. For men who have a diagnosis of mCRPC, the presence of mutations in DNA repair genes is under-recognized and is clinically useful. Standard therapies such as platinum chemotherapy and immunotherapy for MSI-high tumors can be considered in patients harboring DNA repair abnormalities. Additional mutations are on the cusp of demonstrating clinical utility and many future therapies will likely be dependent on the presence of genomic biomarkers. Ongoing research is needed to further define optimal use of germ-line and somatic testing of patients with advanced prostate cancer.

## Kidney Cancer

### Genetic Risk

The Nordic Twin Study of Cancer suggested that kidney cancer showed evidence of heritability, though the familial risk estimation was quite low in dizygotic twins (1). Several genes have been implicated in inherited syndromes that are associated with an increased risk of developing kidney cancer (Table 2). These inherited syndromes represent a small proportion of newly diagnosed renal cancers, but have informed our understanding of the biology of kidney cancer. Unfortunately, no established screening paradigm exists for kidney cancer. Patients with a known inherited syndrome are frequently recommended, based on expert opinion, to undergo annual cross sectional imaging for surveillance with either computed tomography or magnetic resonance imaging of the abdomen.

Table 1. Prostate Cancer Summary

Pathway/Gene	Biologic Role	Clinical Implications
<i>HOXB13</i>	Tumor suppressor gene encoding a DNA-binding domain	Germline mutations confers 4.5 times increased risk of developing prostate cancer; Informs shared decision making for prostate cancer screening; genetic counseling when germline mutation detected
<i>BRCA1</i>	Tumor suppressor gene encoding DNA repair machinery	Germline mutations confers 3.8 times increased risk of developing prostate cancer; Informs shared decision making for prostate cancer screening; genetic counseling when germline mutation detected; more aggressive clinicopathologic disease; potential for treatment with PARP inhibitors and immunotherapy
<i>BRCA2</i>	Tumor suppressor gene encoding DNA repair machinery	Germline mutations confers 8.6 times increased risk of developing prostate cancer; Informs shared decision making for prostate cancer screening; genetic counseling when germline mutation detected; earlier onset and more aggressive clinicopathologic disease; potential for treatment with PARP inhibitors and immunotherapy
AR-V7 splice variant	Confers resistance to next generation anti-androgen therapy	Predicts lack of response to abiraterone/enzalutamide
DNA Damage Response and Repair Pathway ( <i>BRCA2, ATM, CHEK2, BRCA1, RAD51D, PALB2, MSH2, MLH1, MSH6</i> )	Encode for cellular machinery responsible for the recognition and repair of DNA damage	DDR-deficient tumors predict response to immunotherapy with checkpoint inhibitors of the PD1 pathway; may predict response to PARP inhibitors; germline mutations are common and patients should receive genetic counseling when detected
PI3K Pathway ( <i>PTEN, PIK3CA, AKT1, PIK3CB</i> )	Intracellular signaling pathway that regulates cell cycle	May predict benefit to PI3K inhibitors

Table 2. Syndromes Associated with Increased Risk of Renal Cell Carcinoma

Syndrome	Mutation	Clinical Features
<b>Clear Cell Carcinoma</b>		
Von Hippel Lindau	VHL	CNS hemangioblastomas, pheochromocytoma, pancreatic neuroendocrine tumor
PTEN Hamartoma Syndrome	PTEN	Lipomas, fibromas, acral keratosis, GI polyps; increased risk of cancers of the breast, thyroid, and endometrium; papillary renal carcinoma also seen
Familial Clear Cell with Chromosome 3 Translocation	Translocation chromosome 3	Clear cell kidney cancer
BAP1 Mutant Disease	BAP1	Melanoma, mesothelioma, epithelioid atypical Spitz tumors
<b>Papillary Carcinoma</b>		
Hereditary Leiomyomatosis	FH	Cutaneous and uterine leiomyomata; Papillary renal carcinoma type 2
Hereditary Papillary Renal Cancer	MET	Papillary renal carcinoma type 1
<b>Other Histology</b>		
Tuberous Sclerosis Complex	<i>TSC1, TSC2</i>	Facial angiofibromas, subependymal giant cell astrocytoma, subependymal nodules, CNS cortical tubules; renal angiomyolipoma
SDH-associated Renal Cancer	<i>SDHB, SDHC, SDHD</i>	Paraganglioma, pheochromocytoma; renal clear cell, chromophobe, or oncocytoma
Lynch Syndrome	<i>MLH1, MSH2</i>	Familial history of cancer, primarily colon endometrial, ovarian, small bowel, upper urinary tract urothelial carcinoma, pancreatic; clear cell and papillary renal carcinoma described (25)

### **Clinical Decision Making**

Genomic testing currently has no established role in the prognosis and treatment of kidney cancer, though some genomic factors are emerging in clear cell carcinoma of the kidney that may contribute to clinical decision making in the future. Clear cell renal cell carcinoma (ccRCC) is characterized by loss or inactivation of the *VHL* gene (26), located on the short arm of chromosome 3. The development of haplo insufficiency at 3p appears to be an early event in the genetic evolution of ccRCC (27). A second hit to *VHL* typically occurs later in life via mutation or methylation events that result in a decrease or loss of expression of *VHL* (28). This results in downstream signaling changes promoting tumorigenesis. Given the early and nearly ubiquitous presence of *VHL* abnormalities in ccRCC, other genomic markers have been explored as potential prognostic and predictive markers.

Mutations in *PBRM1* and *BAP1*, which are also located on 3p, have been shown to have prognostic utility (29). Expression of *PBRM1* and *BAP1* from resected ccRCC specimens stratified outcomes into four distinct groups. *PBRM1*+/*BAP1*+ specimens had the longest relapse free and disease specific survival, while *PBRM1*-/*BAP1*- tumors had the worst outcomes. These genetic findings correlated with traditional pathologic characteristics that are associated with poor outcomes, such as tumor size, TNM stage, nuclear grade, and tumor necrosis. While this very nicely ties the genetic abnormalities to the biology and clinical features of the disease, it does not provide a superior methodology for estimating risk.

The *MTOR* pathway has been a target of treatment in ccRCC, with both temsirolimus and everolimus approved. Mutations in *TSC1*, *TSC2*, and *MTOR* have been demonstrated in ccRCC, with *TSC1* muta-



tions associated with the development of higher grade tumors (30). These mutations have also been associated with response to mTOR inhibitors (31), which have been approved for use in poor risk patients. Mutations in *PBRM1* have been associated with response to the immune checkpoint inhibitors, though the strength and mechanism of this interaction is unclear (32).

### **Summary**

While our understanding of the genomic factors underlying the clinical behavior of ccRCC has made tremendous progress in the last decade, genomic testing in kidney cancer has little role in the treatment of patients outside the context of clinical trials. A deeper understanding of the genomic alterations driving biological behavior is emerging. In patients with a strong family history of syndromes associated with an increased risk of kidney cancer or clinical characteristics of these syndromes, consideration of germline testing should be given and discussed with the patient.

## **Urothelial Carcinoma**

### **Genetic Risk**

Bladder cancer has evidence of heritable risk factors, though exact genomic mechanisms of this risk are less well understood. Urothelial carcinoma is associated with hereditary non-polyposis colorectal cancer, also known as the Lynch syndrome. Defects in *MSH2* in particular were associated with an increased risk of developing upper tract urothelial carcinoma in a Danish cohort of families with Lynch syndrome (33). Renal pelvis and ureteral urothelial carcinoma is included in the Amsterdam II criteria as a Lynch syndrome-associated cancer. Patients who present with upper tract disease should undergo detailed family history to explore for evidence of heritable mismatch repair defects and have germline testing performed as appropriate (34).

### **Clinical Decision Making**

Molecular subtyping of urothelial cancer utilizing gene expression profiling techniques has emerged as a potential prognostic and predictive tool. Four subtypes emerged from the Cancer Genome Atlas project via a hierarchical clustering analysis, originally described as clusters I, II, III, and IV (35). Clusters I and II refer to luminal subtypes and clusters III and IV to basal subtypes. Other groups have divided the subtypes differently, but similarities exist between the various categories. Basal subtypes have been shown to be more aggressive and are associated with worse survival in chemotherapy-naïve urothelial carcinoma (36). Interestingly, basal subtypes have also been shown to have the best outcomes after administration of neoadjuvant chemotherapy (37). Molecular subtyping may also provide predictive information regarding response to immunotherapy. Utilizing the Cancer Genome Atlas (TCGA) subtyping classification, cluster III subtypes had the highest response rate compared with other subtypes at 30% following treatment with nivolumab in the second line setting (38). Cluster III subtypes were also associated with the strongest interferon- $\gamma$  expression signature, which also correlated with a higher likelihood of response (38). The same TCGA subtyping was utilized in the corresponding clinical trial for atezolizumab following platinum based chemotherapy. Cluster II subtypes showed the best response rate to therapy at 34%. However, PD-L1 expression levels and CD8 T cell gene expression markers were higher in the cluster III subtype (39). These data come from smaller phase II trials and will be explored in larger phase III trials.

In addition to broad molecular subtyping, specific genetic mutations have been identified that may impact clinical decision making. Somatic mutations in the nucleotide excision repair gene *ERCC2* are present in 7-12% of

urothelial carcinoma (35, 40). Mutations in *ERCC2* are associated with a distinct molecular subtype (41) that overlaps with luminal subtypes. The presence of *ERCC2* mutations was enriched in patients who responded to cisplatin chemotherapy (40) and later validated as a biomarker of platinum sensitivity (42). Mutations in other DNA damage response and repair (DDR) machinery have also been identified in urothelial carcinoma as a biomarker of response to immunotherapy. In a series of 60 patients, 46.7% had an alteration in DDR genes with 25% having deleterious alterations (43). Deleterious DDR mutations were found in *ATM*, *POLE*, *BRCA2*, *ERCC2*, *FANCA*, and *MSH6*. The presence of DDR mutations were associated with higher response rates, longer progressive free survival, and longer overall survival with immunotherapy. Mutations in *FGFR3* have been identified as an intriguing target for therapy. Cluster I subtypes are enriched with *FGFR3* mutations (35) and are generally associated with immunologically cold tumors that do not respond to checkpoint inhibitors (38, 39). Small molecule tyrosine kinase inhibitors of *FGFR3* are currently in development and showing promising results. The *FGFR3* TKI

erdafitinib was recently reported in a phase II trial to have an overall response rate of 40% (44). Given that this is a population that has poorer responses to immunotherapy and minimal therapeutic options, erdafitinib represents a potential breakthrough for patients with urothelial cancer.

### Summary

Urothelial carcinoma has some association with the Lynch syndrome, especially when presenting with upper urinary tract disease, and a detailed family history should be obtained in these patients. Referral to genetic counselor may be warranted if history suggests the presence of a heritable syndrome. Molecular profiling of urothelial carcinoma has revealed distinct subgroups of disease with differing clinical behavior. There are early signs that molecular subtyping may play a role in prognosis and treatment selection (Table 3), but this is currently not applicable outside the clinical trial setting. *ERCC2* mutations are useful in predicting response to platinum chemotherapy, are not specific enough to warrant omitting administration of cisplatin to patients who are oth-

Table 3. Urothelial Cancer Summary

TCGA Molecular subtyping		
Pathway/Gene	Biologic Role	Clinical Implications
<i>Cluster I</i>	Luminal subtype	Less aggressive, less benefit from neoadjuvant chemotherapy
<i>Cluster II</i>	Luminal subtype	Less aggressive, less benefit from neoadjuvant chemotherapy; higher response rates to atezolizumab
<i>Cluster III</i>	Basal subtype	More aggressive, better response to neoadjuvant chemotherapy; higher response rates to nivolumab
<i>Cluster IV</i>	Basal subtype	More aggressive, better response to neoadjuvant chemotherapy
DNA Damage Response and Repair Pathway ( <i>ATM</i> , <i>POLE</i> , <i>BRCA2</i> , <i>ERCC2</i> , <i>FANCA</i> , <i>MSH6</i> )	Encode for cellular machinery responsible for the recognition and repair of DNA damage	Higher response rates to checkpoint inhibitors
<i>ERCC2</i>	Nucleotide excision repair	Predicts higher response rates to cisplatin
<i>FGFR3</i>	Fibroblast growth factor receptor	Predicts response to <i>FGFR3</i> tyrosine kinase receptor inhibitors (erdafitinib)

TCGA=The Cancer Genome Atlas.

erwise eligible. This is also true of defects in DDR genes as they relate to administration of checkpoint inhibitors. *FGFR3* alterations will likely become a key piece of information, as targeted therapy is likely to be approved for patients with these alterations in the near future pending completion of phase III studies.

## Conclusions

Clinical breakthroughs resulting from a deeper understanding of the genetic influences in cancer have been a leap forward in the field of oncology. Genitourinary malignancies have not felt the impact as significantly. Breast and thoracic malignancies are prime examples of the potential power of genomic data, as genomic data influences decisions on treatment in a large proportion of patients. Genomic data is currently most relevant in identifying patients carrying high risk germline alterations for genitourinary cancers. The role of genomic testing to influence treatment decisions is currently limited. Fortunately, the field is changing rapidly and breakthroughs driven by genomic information are on the horizon.

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