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# Outcomes of Genetic Testing in a Genitourinary Genetics Clinic

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# OUTCOMES OF GENETIC TESTING IN A GENITOURINARY GENETICS CLINIC

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OUTCOMES OF GENETIC TESTING IN A GENITOURINARY GENETICS CLINIC

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Several known hereditary cancer syndromes confer an increased risk for genitourinary (GU)related malignancies. Various guidelines indicate when to refer patients to genetic counseling for GU-related hereditary cancer syndromes but there is limited research on the clinical picture of these patients, including their cancerous and non-cancerous features, the genetic testing strategy for this population, and the probability of having a positive germline mutation if testing is performed. The purpose of this study is to determine the most common indications for ordering genetic testing in a GU Genetics Clinic and evaluate whether there is a relationship between the indication for genetic testing and genetic testing outcome. An institutional review board-approved retrospective chart review was performed for 220 patients seen in the GU Genetics Clinic at M.D. Anderson Cancer Center. Patients were stratified into groups based on their indication for genetic testing and an exact binomial test was used to compare the proportion of patients with a positive genetic test from various groups. The majority of patients (92%) were seen for genetic evaluation related to either renal cell carcinoma (RCC) or prostate cancer. Among patients seen for RCC-related evaluation (N=107), meeting published clinical criteria for a hereditary RCC syndrome significantly predicted positive genetic testing ($P$<0.001). No other indication for testing, including early onset RCC (diagnosed ≤ 46 years) predicted for positive genetic test results. Among patients seen for

prostate-related evaluation (N=101), 7 individuals tested positive for a hereditary syndrome related to prostate cancer, however none were identified by metastatic prostate cancer status alone. Our data suggest current algorithms lack sensitivity for selecting individuals with RCC or prostate cancer at risk for germline mutations. Evaluation of pedigree and identifying presence of syndromic features can guide risk assessment and increase the probability of identifying individuals with GU cancers at risk for harboring a germline cancer causing mutation.

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## INTRODUCTION

Cancers of the genitourinary (GU) system include prostate, renal, urinary tract, testicular, and bladder cancer. The known hereditary components and the relatively high incidence of particular GU cancers make them a relevant subset of cancers in the setting of a genetic evaluation. Prostate cancer is the most common cancer diagnosis in men in the United States (1). It is estimated that 5-10% of prostate cancers are due to inherited pathogenic variants in highly penetrant or moderately penetrant genes (2). Aggressive cases of prostate cancer, in particular, have a higher association with an inherited predisposition, with 11.8% of metastatic prostate cancers resulting from a pathogenic germline variant in DNA- damage repair (DDR) genes (3). Renal cancer is similarly known to be associated with inherited pathogenic variants. Conservative estimates predict that 5% to 8% of renal cell carcinoma (RCC) is hereditary (4).

Several known hereditary cancer syndromes confer an increased risk for GU-related malignancies. Pathogenic variants in *BRCA1* and *BRCA2,* causing Hereditary Breast and Ovarian Cancer syndrome (HBOC), make up over 50% of the pathogenic variants found in DDR genes among men with metastatic prostate cancer (3). The National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment- Breast and Ovarian Guidelines provide criteria for when to evaluate patients for HBOC. These guidelines consider both personal and family history of prostate cancer, especially when combined with cases of breast and/or ovarian cancer in a family (5). Just as HBOC causes hereditary cases of prostate cancer, at least eight different syndromes predispose to RCC including von Hippel-Lindau (VHL) disease, hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dube syndrome (BHD), hereditary leiomyomatosis and renal cell carcinoma (HLRCC), succinate dehydrogenase-deficient kidney cancer, Tuberous Sclerosis Complex (TSC), *BAP1*-associated tumor predisposition syndrome, and MiTF-associated cancer syndrome (6). Some of these syndromes are highly associated with non-cancerous features that aid

in the identification of affected individuals. VHL disease is associated with a high penetrance for retinal and central nervous system hemangioblastomas in addition to clear cell renal cell carcinoma (ccRCC) (7-9). Individuals with HLRCC present with multiple or symptomatic leiomyomas and early onset type 2 papillary RCC (10). Fibrofolliculomas and spontaneous pneumothoraces are indicative of BHD (11). TSC has a very well- defined phenotypic presentation with multiple major and minor features contributing to a clinical diagnosis (12).

Many indications may warrant a genetic evaluation for patients with GU cancers. Practice guidelines published by the American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors (NSGC) support that referral of GU cancer patients for a genetics consultation is indicated in the context of both personal and family history. The ACMG/NSGC guidelines for RCC patients encompass high-risk factors such as bilateral or multifocal ccRCC, ccRCC in the context of a family history of ccRCC, renal tumor histology suggestive of a hereditary syndrome (e.g. any papillary type II RCC being suggestive of HLRCC), upper tract urothelial carcinoma (UTUC) in the context of a family history of Lynch syndrome associated cancers, and RCC in the context of other RCC-related syndromic features. The ACMG/NSGC guidelines for prostate cancer include high-risk factors such as family history of prostate cancer in first degree relatives, family history of early onset prostate cancer, and aggressive (Gleason score>7) prostate cancer in the context of a family history of breast, ovarian, or pancreatic cancer (13). Published research also suggests that genetic counseling or consideration of germline testing is indicated for some individuals, despite the absence of non-cancerous findings and/or family history, due to factors that put them at an increased risk for a hereditary cancer predisposition. One of these high-risk factors is RCC diagnosed ≤46 years old, as early onset RCC may be a sign of a hereditary syndrome (4). Another high-risk factor in the setting of GU cancers is

metastatic prostate cancer. Recent research suggests that all men with metastatic prostate cancer should undergo germline genetic testing of DDR genes (3, 14).

Multiple studies on genetic testing outcomes of RCC patients suggest that early onset RCC is a significant predictor of positive genetic testing (15, 16). Other factors believed to predict positive genetic test results are non-cancerous manifestations of RCC syndromes and multiple primary renal tumors. The significance of family history of RCC in predicting at-risk individuals has been questioned (15, 16). Studies of genetic testing outcomes in men with prostate cancer support that those meeting NCCN guidelines for HBOC testing are at the highest risk for mutations yet recognize that many men perceived to have a hereditary prostate cancer may not have an identifiable gene mutation (14). The literature effectively describes when to refer patients for genetic counseling for GU-related hereditary cancer syndromes, however there is limited research on the clinical picture of these patients, including their cancerous and non-cancerous features and indications for genetic testing (3-5, 13). Previous studies of this population have not commented on whether individual indications, independent of one another, predict positive germline testing. Additionally, the genetic testing strategy and decision-making process in a GU genetics clinic has not been described.

This study aims to assess the most common indications for ordering genetic testing in a GU setting. Additionally, the study aims to evaluate whether there is a relationship between the indication for genetic testing and genetic testing outcome. To do so, a retrospective chart review was conducted of test results and clinical data from patients seen for genetic counseling in the Genitourinary Genetics Clinic at The University of Texas M.D. Anderson Cancer Center.

## METHODS

Institutional Review Board approval was obtained for a retrospective chart review of 220 patients seen for genetic counseling at M.D. Anderson Cancer Center's Genitourinary Genetics Clinic between July 1, 2014 and June 30, 2017. All patients had either a personal history of a GU cancer (RCC, prostate, UTUC, testicular, or bladder), family history of GU cancer(s), personal history of non-cancerous findings suggestive of a GU-related hereditary cancer syndrome, or family history of a germline pathogenic variant in a gene causing a hereditary cancer syndrome. GU-related hereditary cancer syndromes with non-cancerous findings considered in this study include BHD, HLRCC, VHL disease, and TSC, as these syndromes have published clinical diagnostic criteria. All patients in this clinic underwent genetic counseling and formal genetic assessment for hereditary cancer syndromes including potential evaluation of both benign and malignant features. As part of the genetic counseling process, a three generation pedigree was obtained for each patient to evaluate cancer histories in the family.

Each patient's medical and family histories were assessed to determine whether genetic testing was indicated based on published literature and whether genetic testing was ordered. Assessment of family history included reviewing each patient's pedigree in order to determine the family's cancer history and familial RCC or familial prostate cancer status (defined as two or more relatives of the same lineage, not including the patient, with the same type of cancer) (17). When applicable, the type of genetic testing ordered and result of genetic testing were recorded.

Genetic testing was considered to be indicted based on personal history if the patient had any of the following: a clinical diagnosis of VHL disease, a clinical diagnosis of TSC , a suspected diagnosis of BHD, a likely or suspected diagnosis of HLRCC, early onset RCC (≤46 years), metastatic prostate cancer , or personal features meeting ACMG/NSCG Practice Guidelines for referral to genetic counseling for prostate or renal cancer (henceforth known as ACMG/NSGC

guidelines). ACMG/NSGC guidelines indicate only when patients should be referred for a genetic counseling evaluation, not when to order genetic testing. However, in the context of limited guidelines for genetic testing in the GU cancer population, this study evaluated ACMG/NSGC guidelines as if they were an indication for genetic testing. Genetic testing was considered to be indicted based on family history if the patient had any of the following: a reported familial germline pathogenic variant in a gene causing a hereditary cancer syndrome, family history meeting NCCN *BRCA*-Related Breast and Ovarian Cancer Syndrome testing criteria (versions 1.2014- 2.2017), or family history meeting ACMG/NSCG guidelines. For each patient, the specific version of NCCN *BRCA*-Related Breast and Ovarian Cancer Syndrome guidelines valid at the time of their genetic counseling consultation was considered.

Genetic testing type was categorized as single site, single syndrome, or panel testing. Single syndrome genetic testing may have included testing more than one gene related to a given syndrome, such as testing both *BRCA1* and *BRCA2* under the category of HBOC. Genetic testing results were recorded as positive, negative, variant of uncertain significance (VUS)- likely pathogenic, VUS, and VUS-likely benign. "Positive" genetic testing henceforth includes both positive and VUS-likely pathogenic results in order to mimic the treatment of these results in a clinical setting. Similarly, "negative" testing includes negative and VUS-likely benign results. In this population, true VUS results did not change medical management for any patients. Therefore, patients with VUS results from germline testing were categorized with the negative group during the evaluation of the relationship between indication for testing and genetic testing outcome. Tables where VUS results have been included in the negative category are indicated as such.

The total population was stratified into three groups: 1) patients seen for genetic evaluation of hereditary cancer syndromes related to RCC, 2) patients seen for genetic evaluation of hereditary cancer syndromes related to prostate cancer, and 3) patients seen for genetic evaluation of other GU

cancers. These groups were not mutually exclusive as some patients were seen for evaluation of both renal and prostate cancer and were included in both groups.

Patients were stratified by indication for genetic testing and the rate of positive genetic test results was reported for each group. The statistical relationship between indication for genetic testing and genetic testing outcome was determined using the Pearson chi-square and exact chi-square tests with $P<0.05$ considered to be statistically significant. Statistical analysis was performed using STATA/IC version 13.1 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). All tests of statistical significance utilized SAS.

## RESULTS

A total of 220 patients were seen for genetic counseling in the GU Genetics Clinic between July 1, 2014 and June 30, 2017. All 220 patients were included in this study. The majority of the population was Caucasian (76%) and 4% reported Ashkenazi Jewish ancestry. Population demographics are summarized in Table 1. A total of 201 patients (91%) had a diagnosis of cancer

**Table 1** Demographic Information

| Characteristic | Frequency | Percent | Cumulative |
|---|---|---|---|
| **Sex** | | | |
| Male | 169 | 23.18 | 23.18 |
| Female | 51 | 76.82 | 100.00 |
| **Ethnicity** | | | |
| Hispanic or Latino | 34 | 15.45 | 15.45 |
| Not Hispanic or Latino | 179 | 81.36 | 96.82 |
| Unknown | 7 | 3.18 | 100.00 |
| **Race** | | | |
| White or Caucasian | 166 | 75.45 | 75.45 |
| Black or African American | 13 | 5.91 | 81.36 |
| Asian | 9 | 4.09 | 85.45 |
| Other | 24 | 10.91 | 96.36 |
| Unknown | 8 | 3.64 | 100.00 |
| **Ashkenazi Ethnicity** | | | |
| Ashkenazi | 8 | 3.64 | 3.64 |
| Not Ashkenazi | 212 | 96.36 | 100.00 |

(any type) with 158 having a single cancer diagnosis, 33 having two primary cancer diagnoses, and 10 having three or more primary cancer diagnoses. There were 86 patients (39%) with a diagnosis of RCC, 8 of whom had two primary diagnoses of RCC, giving a total of 94 individual RCC diagnoses. The average age of RCC diagnosis was 45 years old (20-72 years). The majority of RCCs were clear cell type (66%) followed by chromophobe, papillary type II, oncocytoma type, and papillary type 1. Five patients had mixed RCC histology. A total of 99 patients (45%) had a diagnosis of prostate cancer, of whom 56 were confirmed metastatic and 78 were aggressive (Gleason $\geq 7$). The average age of prostate cancer diagnosis was 59 years old (41-82 years).

Additionally, 11 patients had UTUC, 9 patients had bladder cancer, and 1 patient had testicular cancer (Table 2).

**Table 2** Oncologic Information

| Cancer Type | Frequency | Percent | Cumulative |
|---|---|---|---|
| **Renal cell carcinoma** | | | |
| ALL | 94 | 100.00 | |
| Clear cell | 62 | 65.96 | 65.96 |
| Papillary type I | 3 | 3.19 | 69.15 |
| Papillary type II | 6 | 6.38 | 75.53 |
| Chromophobe | 7 | 7.45 | 82.98 |
| Oncocytoma | 5 | 5.32 | 88.30 |
| Papillary Unspecified | 6 | 6.38 | 94.68 |
| Mixed | 5 | 5.32 | 100.00 |
| **Prostate** | | | |
| ALL | 99 | 100.00 | |
| Gleason score ≥ 7 | 78 | 78.79 | 78.79 |
| Gleason score <7 | 16 | 16.16 | 94.95 |
| Gleason score unknown | 5 | 5.05 | 100.00 |
| Metastatic | 56 | 56.67 | 56.67 |
| Not metastatic | 43 | 43.43 | 100.00 |
| **UTUC** | 11 | | |
| **Bladder** | 9 | | |
| **Testicular** | 1 | | |

In total, 194 individual genetic tests were ordered for 174 patients and 27 germline mutations were identified (14% rate of positivity). A VUS was identified in 23 patients (12%). The most common type of testing ordered was multi-gene panel testing (59%) followed by single syndrome (36%), and single site testing (5%). Multi-gene panel testing yielded positive results in 9% of tests and had a VUS rate of 19%. Single syndrome testing yielded positive results in 17% of tests with a VUS rate of less than 1%.

The majority of patients (203 of 220, 92%) were referred for evaluation of syndromes related to RCC or prostate cancer. There were 102 patients with RCC-related referrals, 96 with prostate-related referrals, and 5 patients seen for evaluation of both RCC and prostate-related hereditary cancer syndromes. In 2014 and 2015, the majority of referrals were RCC-related (83%

and 71% respectively). In 2016 and 2017, the majority of referrals were prostate-related (52% and 68% respectively).

There were 107 patients in the RCC-related referral group (including the 5 patients with overlapping RCC and prostate indications). Genetic testing was ordered for 97 patients in this population and 16 tested positive for a hereditary cancer syndrome related to RCC. Six mutations were identified in the *FH* gene, 5 in the *FLCN* gene, 3 in the *VHL* gene, 1 in the *BAP1* gene, 1 in the *SDHB* gene, and 1 in the *TP53* gene. The indications for genetic testing in this group are summarized in Table 3. Patients may have had more than one indication for ordering genetic testing. In this group, 60 of the 97 patients who had genetic testing (62%) met ACMG/NSGC guidelines, making this the most common indication for testing. Of the 9 distinct criteria that make up ACMG/NSGC guidelines for RCC, the most commonly met criterion, seen in 67% of the 60 patients meeting guidelines, was "RCC with clear cell histology AND dx at age <50 OR bilateral or multifocal tumors OR ≥1 close relative with clear cell RCC" (13). In bivariate analysis, meeting published clinical criteria for an RCC syndrome significantly predicted a positive test result ($P$<0.001), but meeting ACMG/NSGC guidelines, diagnosis ≤ 46, and presence of familial RCC did

**Table 3** Indications for Genetic Testing in RCC-Related Referral Group

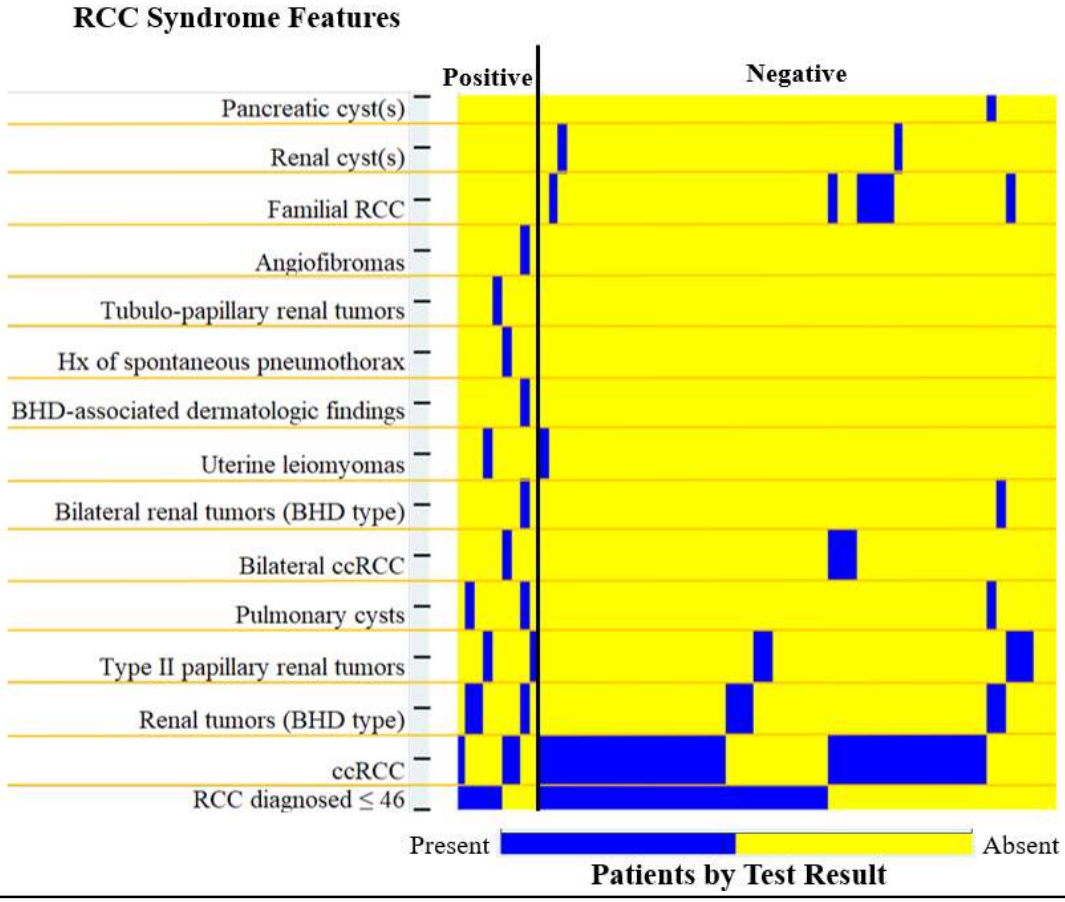
| | All RCC-related referral patients (n=107) | | Test Result: Any Testing (n=97) | | Positive | | *Negative | | ***P* value** |
|---|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | |
| All | 107 | (100%) | 97 | (100%) | 16 | (16%) | 81 | (84%) | |
| **Testing Indication Met** | | | | | | | | | |
| ANY RCC-related syndrome criteria | 12 | (11%) | 12 | (12%) | 7 | (58%) | 5 | (42%) | **<0.001** |
| ACMG/NSGC RCC Guidelines | 60 | (56%) | 60 | (62%) | 7 | (12%) | 53 | (88%) | **0.10** |
| RCC diagnosed ≤ 46 | 44 | (41%) | 42 | (43%) | 5 | (12%) | 37 | (88%) | **0.29** |
| No testing criteria met | 29 | (27%) | 21 | (22%) | 1 | (5%) | 20 | (95%) | **0.18** |
| Familial RCC | 12 | (11%) | 12 | (12%) | 1 | (8%) | 11 | (92%) | **0.68** |

*Negative column includes true VUS results

not. Twenty-four (24) patients diagnosed at ≤ 46 years had no additional syndromic features or family history and none in this group tested positive for a germline mutation. In comparison, 18 patients diagnosed at ≤ 46 years had either syndromic features and/or a pedigree suggestive of an RCC syndrome and 5 of them tested positive for a germline mutation.

Figure 1 depicts the frequency of the cancerous and non-cancerous features seen in this clinic among patients in the RCC-related referral group who tested positive and who tested negative. The figure shows that patients who had early onset RCC and positive germline testing had additional finding contributing to their risk assessment other than their age of RCC diagnosis. Conversely, none of the patients with early onset ccRCC as their sole criterion had a positive germline test.

**Figure 1** Frequency of RCC Hereditary Syndrome Features Among RCC-Related Referral Group



There were 101 patients in the prostate-related referral group. Genetic testing was ordered for 70 patients in this population and a mutation was identified in 7 of them. There were 5 mutations in the *BRCA2* gene and 2 mutations in the *ATM* gene. The indications for ordering genetic testing are summarized in Table 4. The most common indication for ordering genetic testing was having metastatic prostate cancer (39 of 70, 56%) followed closely by meeting NCCN guidelines for HBOC (37 of 70, 53%). ACMG/NSGC guidelines for prostate cancer were also cited as an indication for testing in 21% of patients in this group. All 15 men meeting ACMG/NSGC guidelines met the same criterion within the guidelines: "aggressive (Gleason>7) prostate cancer and ≥2 cases of breast, ovarian, and/or pancreatic cancer in close relatives" (13). Bivariate analysis revealed that none of the indications for genetic testing in the prostate-related referral group (meeting NCCN criteria for HBOC, meeting ACMG/NSGC guidelines, personal history of metastatic prostate cancer, or presence of familial prostate cancer) significantly predicted a positive test result. There were 16 men with metastatic prostate cancer as their only indication for genetic testing and no germline mutations were identified in this group. In comparison, 23 patients had

**Table 4** Indications for Genetic Testing in Prostate-Related Referral Group

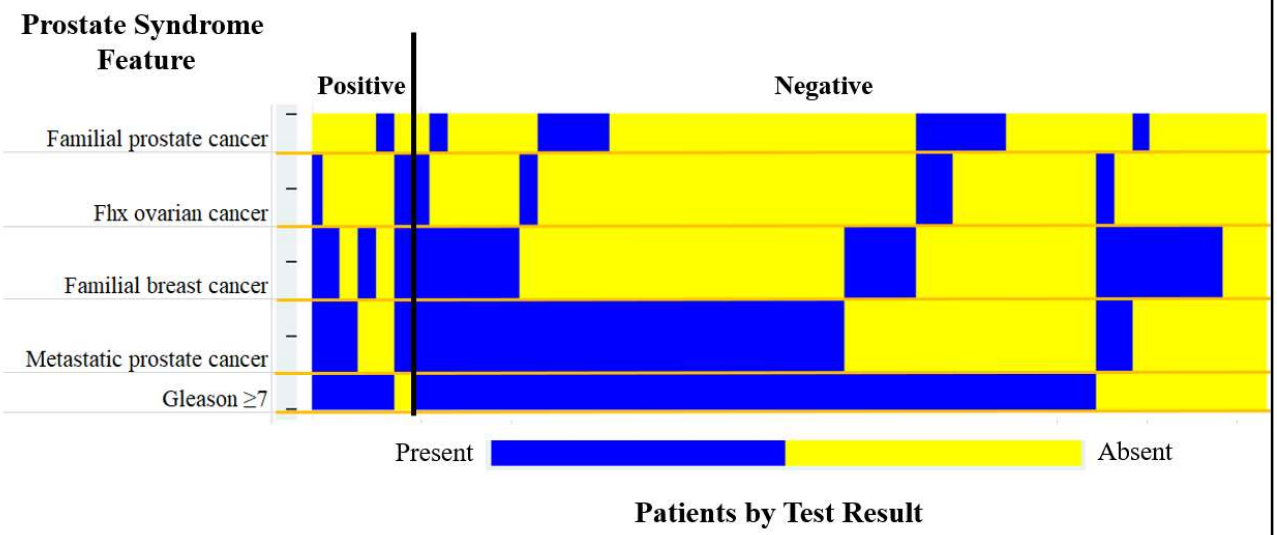
| | All prostate-related referral patients (n=101) | | **Test Result** | | | | ***P* value** |
|---|---|---|---|---|---|---|---|
| | | | Any Testing (n=70) | | Positive | *Negative | |
| | **N** | **%** | **N** | **%** | **N %** | **N %** | |
| All | 101 | (100%) | 70 | (100%) | 7 (10%) | 63 (90%) | |
| **Testing Indication Met** | | | | | | | |
| NCCN Guidelines for HBOC | 43 | (43%) | 37 | (53%) | 6 (16%) | 31 (84%) | **0.11** |
| ACMG/NSGC Prostate Cancer Guidelines | 15 | (15%) | 15 | (21%) | 1 (7%) | 14 (93%) | **>0.99** |
| Metastatic prostate cancer | 56 | (55%) | 39 | (56%) | 4 (10%) | 35 (90%) | **>0.99** |
| No testing criteria met | 23 | (23%) | 12 | (17%) | 1 (8%) | 11 (92%) | **>0.99** |
| Familial PrCa | 18 | (18%) | 16 | (23%) | 2 (13%) | 4 (88%) | **>0.99** |

*Negative column includes true VUS results

metastatic prostate cancer in addition to a relevant family history of either prostate, breast, or ovarian cancer and 4 were found to have germline mutations.

Figure 2 shows the frequency of features that suggest a hereditary cancer syndrome for patients in the prostate-related referral group. This figure shows that all men with aggressive, metastatic prostate, in the absence of a relevant family history or additional indication for genetic testing, had negative germline testing. Of note, a single patient lacking family history may be seen in the positive section, however this patient had a known familial mutation (Appendix A).

**Figure 2** Frequency of Hereditary Syndrome Features Related to Prostate Cancer Among Prostate-Related Referral Group



## DISCUSSION

This is the first study to describe clinical features and genetic testing outcomes of a patient cohort referred to a GU Genetics Clinic that is following current guidelines for germline genetic testing. Patients were referred to genetic counseling in this setting primarily for evaluation of hereditary cancer syndromes related to RCC and prostate cancer. A minority group of patients were referred for genetic evaluation of other GU cancer types, including UTUC, bladder cancer, and testicular cancer. A shift in referrals to this GU Genetics Clinic was seen over the course of the collection period. There were significant changes in published recommendations for genetic evaluation of men with prostate cancer during the time that this patient population was assessed. Most notably, a study published in August, 2016 recommended genetic testing for all men with metastatic prostate cancer, regardless of age of diagnosis or family history (3). This significant change in guidelines likely contributed to the shifting referral pattern noted between 2014 and 2017.

In the RCC population, three overarching indications drove genetic testing for patients with an RCC-related referral: meeting published clinical diagnostic criteria for an RCC-related hereditary cancer syndrome, meeting ACMG/NSGC guidelines for RCC, and being diagnosed with RCC $\leq$ 46 years old. Meeting ACMG/NSGC guidelines was the most commonly indicated reason for ordering genetic testing, likely due to the nature of these guidelines being comprised of multiple individual indications for testing. For example, a patient with bilateral ccRCC, a patient with papillary type II RCC, and a patient with chromophobe RCC would all meet these guidelines for different reasons. However, meeting ACMG/NSGC guidelines did not predict positive germline testing for an RCC syndrome ($P$=0.10). It is important to highlight, again, that these guidelines are not intended to determine when a clinician should order genetic testing, but only when a patient should be referred for genetic evaluation. These guidelines aim to catch all individuals who may be at risk for an RCC-related hereditary cancer syndrome, therefore valuing the sensitivity of the guidelines over the

specificity. This contributes to the failure to show a significant relationship between meeting these guidelines and testing positive. Furthermore, it underscores the value of the genetic counseling process to identify the patients meeting these guidelines who warrant genetic testing.

In our patient population, early onset RCC was not a predictor of positive germline testing. This is in contrast to the findings of previous studies suggesting that early onset RCC is suggestive of hereditary RCC syndromes (4, 15). In fact, 88% of patients with early onset RCC in our cohort did not have an identifiable mutation and the 12% who tested positive for a germline mutation had additional features that were suggestive of the syndrome they tested positive for, including non-cancerous features or abnormal immunohistochemistry (IHC) staining (Appendix A). Our study also identified 22 patients with very young RCC (defined using a previously published 2.5% threshold of diagnosis at ≤36 years) who received multi-gene panel testing (4). Again, in the absence of additional suggestive features, none of them tested positive, despite an expected inherited component due to their very early age of RCC diagnosis. Among hereditary RCC syndromes, VHL disease is thought to have the earliest median age of RCC onset at 38.9 to 44 years old (18, 19). Similarly, the median age of onset for HLRCC is 44 years old (20). However, even VHL disease and HLRCC do not adequately account for the very young RCC population, especially when these patients present without syndromic features or family history. It is likely that there are unidentified genes or genetic factors that are contributing to these very young, isolated RCC diagnoses and current testing strategies are ineffective at identifying them.

The only indication in our cohort that significantly predicted positive germline testing was meeting published clinical criteria for an RCC-related syndrome. This is perhaps not surprising given the strict nature of published guidelines. Among the 16 patients who tested positive in the RCC-related referral group, 3 had testing for known familial mutations. The additional 13 patients either met published clinical diagnostic criteria for an RCC-related syndrome or met ACMG/NSGC

guidelines. In Figure 1, the left portion of the heat map, corresponding to patients testing positive, shows the presence of multiple cancerous and non-cancerous features, even in patients with early onset RCC. In contrast, the right portion of the map, corresponding to patients with negative genetic testing, shows large areas lacking coloration, highlighting all of the patients with early onset RCC as their sole indication for testing. No positive patient in this population was identified solely by age at diagnosis, again raising the question of whether very young RCC diagnoses, in the absence of additional indications for testing, are described by any of the known RCC-related syndromes or genes.

In a clinical setting, early onset RCC coupled with a rare tumor histology or syndromic features should warrant genetic testing, even if the patient does not meet strict clinical diagnostic criteria for the suspected RCC-related syndrome. Of the 16 patients who tested positive in our RCC population, 5 of them did not meet strict clinical criteria for the syndrome they tested positive for, although they did have non-cancerous findings suggestive of the syndrome (Appendix A). Some RCC syndromes, such as BHD, may require updated clinical diagnostic criteria since it is now known that characteristic renal tumors or pulmonary findings may sometimes be the presenting features of this condition, rather than dermatologic findings (21).

Genetic testing may still be warranted for individuals with only early onset RCC, but pretest counseling, including a thorough risk assessment and discussion of the limitations of genetic testing, becomes even more critical in these cases. Additional research on the value of performing multi-gene panel testing on patients with very early onset RCC in the absence of accompanying syndromic features or positive pedigree must be performed to determine whether this approach is valid. Gene hunting studies incorporating whole exome sequencing are also warranted for this patient population due to our perceived lack of knowledge on the genetic contributions to RCC.

Similar to the RCC-related referral group, three general indications for genetic testing were evaluated in the prostate-related referral group: meeting NCCN guidelines for Breast and Ovarian Cancer syndrome, meeting ACMG/NSGC guidelines for prostate cancer, and presence of metastatic prostate cancer. The most common indication for ordering genetic testing was having metastatic prostate cancer (39 of 70 patients tested, 56%), followed closely by meeting NCCN guidelines for HBOC (37 of 70 patients tested, 53%). All patients were seen prior to the inclusion of metastatic prostate cancer as a criterion for meeting NCCN guidelines for HBOC. Additionally, some men in this study were seen before metastatic prostate cancer was considered an independent indication to perform genetic testing in the absence of a family history of HBOC-associated cancers. This contributed to the lower number of individuals who pursued genetic testing in this group. Retrospectively, it was identified that 56 men had metastatic prostate cancer and therefore meet current guidelines for genetic testing. However, that was not, by itself, an indication for testing in all 56 men at the time of their genetic counseling consultation.

In the prostate-related referral group, no significant relationships between indication for genetic testing and positive genetic test results were identified. The small number of patients who tested positive in this group was a limiting factor of the analysis. Of the 7 prostate-related patients who tested positive, 6 of them met NCCN guidelines for HBOC testing. A single patient was identified to have a *BRCA2* mutation without meeting any guidelines for genetic testing. This patient desired genetic testing due to the presence of familial, late-onset prostate cancer but no other family history of cancer. No patient in this study had a germline mutation identified due to the presence of metastatic prostate cancer alone.

It is important to note, however, that 25 of the 70 men who underwent genetic testing in the prostate-related referral group had single syndrome testing for HBOC only (*BRCA1, BRCA2)*. Single syndrome testing may have been the only testing indicated for many patients at the time of

their genetic counseling consultation. It has been suggested that germline mutations in 16 different DDR genes can contribute to metastatic prostate cancer, supporting the use of multi-gene panel testing in this population (3). Our study only identified mutations in *BRCA2* and *ATM* within the prostate group, which may reflect the higher proportion of hereditary prostate cancers attributed to these two genes but it may also reflect the limited genetic analysis in our population.

Thorough pretest counseling is incredibly valuable in this group, similar to the RCC-related group. Multi-gene panel testing should be considered for men with metastatic prostate cancer but should include a discussion of the likely reduced chance of testing positive if the patient does not have any additional family history of HBOC-associated cancers. The recent Philadelphia Prostate Cancer Consensus Conference (2017) revealed a moderate consensus (50-74% consensus) among participants to use multi-gene panel testing for all men with metastatic castration-resistant prostate cancer, regardless of family history, but a stronger consensus (≥75% consensus) to test only *BRCA1* and *BRCA2* in the same scenario, which highlights the varying opinions of experts in the field regarding genetic testing in this population (22).

Finally, this study identified that a combination of testing strategies, including both single syndrome testing and multi-gene panel testing, was utilized in this clinic. Overall, a GU cancer population may be a very good fit for this combination approach to genetic testing in part because RCC syndromes are characteristically different from one another. A patient with BHD, for example, would likely have a tumor histology or non-cancerous features that are very descriptive of BHD and also very distinct from another RCC syndrome. Single syndrome testing is valuable in an RCC population because it is possible to distinguish between RCC syndromes based on clinical findings. Single syndrome testing, when applicable, also comes with the added benefit of a low VUS rate (less than 1% in this study). However, a GU cancer population will also include many patients with prostate cancer. It is much more challenging to differentiate between hereditary syndromes related

to prostate cancer. This is because the features that are suggestive of these syndromes are primarily family history feaures that may be seen in multiple prostate-related syndromes or even in people with no hereditary cancer syndrome at all. In Figure 2, the patients in the positive group are suspicious for a syndrome because they have multiple features suggesting a syndrome. However, it would be hard to distinguish the *BRCA2* positive patients from the *ATM* positive ones based on the family history features listed.

Single syndrome testing has drawbacks, primarily that a clinician cannot rule out the presence of mutations in the genes that were not tested. While this limitation should be considered when chooseing the type of genetic testing to order, the impact of a VUS result on a patient should be considered as well. One study of patient perceptions of VUS results in an oncology setting reported that 29% of patients receiving VUS results recalled their genetic testing being pathogenic, and over half of the 29% underwent potentially unnecessrary prophylactic surgery as a result of their misunderstanding (23). This also suggests that genetic test results, especially VUSs, may be misunderstood by patients' other physicians, such as their surgeons. A study of pediatric oncologists found that only 27% were confident in interpreting and discussing germline genetic testing with patients (24). Given these concerns, it is important to use a risk assessment and pretest counseling to determine the best testing strategy for each patient. In a GU setting especially, there is a place for both multi-gene panel testing and single syndrome testing when a thorough three generation pedigree and evaluation of cancerous and non-cancerous features is used to guide risk assessment.

Small sample size limits the applicability of this study to a larger population. The purpose of this paper was to describe the overall population seen in a GU Genetics Clinic, however additional studies focusing on RCC and prostate cancer populations individually are warranted in order to

increase sample size. Specifically, this study supports a need to further evaluate genetic testing outcomes in patients with very young RCC diagnoses.

The evaluation of clinical data introduces limitations as well. Not all patients in the RCC-related referral group and prostate-related referral group received the same genetic test since the type of testing was decided upon by the patient and the genetic counselor as part of the genetic counseling session. Additionally, multi-gene panels changed and expanded over the course of this study (Appendix B). Clinical information is also limited by the ability of the patients to accurately self-report family history, including ages of cancer diagnoses and, specifically in the case of an RCC-related evaluation, presence or absence of syndromic features in family members. However, this study provided an in-depth evaluation of patients' personal and family history and assessment of specific syndromes. The clinical perspective provided by this study design was invaluable as it allowed detailed analysis of the reasons for genetic testing in a GU cancer population, which has not been commented on previously.

## CONCLUSION

This study described a GU Genetics Clinic that evaluated patients for primarily RCC and prostate-related hereditary cancer syndromes. Pretest counseling for genetic testing in this population is critical considering the varying indications that are present. Patients seen for evaluation of RCC-related syndromes should be assessed for non-cancerous features and family history of RCC. Meeting clinical diagnostic criteria for an RCC-related syndrome predicts for positive germline test results. Genetic testing should be considered for patients with early onset RCC and syndromic features, even in the absence of meeting established clinical diagnostic criteria. Individuals with early onset RCC and no additional features in their risk assessment should be counseled on the limitations of genetic testing for this indication and further assessment of the genetic contributions to RCC is required. Prostate cancer patients may benefit from multi-gene panel testing based on previous studies but will also benefit from pretest counseling on the reduced likelihood to test positive if they lack a family history of relevant cancers. Genetic testing in a GU population should incorporate both single syndrome testing and multi-gene panel testing to accommodate the varying levels of risk assessment.

# APPENDIX

## Appendix A Clinical Features of Patients with Positive Germline Test Results

| Age at Dx | Sex | Mutation | Test Type | Features in Patient / Features in Relatives[1] | Syndrome Criteria | ACMG/ NSGC Guidelines | RCC Dx ≤ 46 | Familial RCC | mPrCa | Familial PrCa |
|---|---|---|---|---|---|---|---|---|---|---|
| **RCC-Related Referral Group** | | | | | | | | | | |
| 29 | M | *FH* | Single site | Tubulopapillary RCC | x | x | ✓ | x | NA | x |
| NA | F | *FH* | Single site | | x | x | NA | x | NA | x |
| NA | F | *FH* | Single site | Uterine leiomyomas / Uterine leiomyomas | HLRCC | x | NA | x | NA | x |
| 40 | F | *FH* | Single syndrome-HLRCC | Papillary type II RCC<br>Uterine leiomyomas | x | ✓ | ✓ | x | NA | x |
| NA | M | *FLCN* | Single syndrome-BHD | Fibrofolliculoma<br>Spontaneous pneumothorax | BHD | x | NA | x | NA | x |
| 47 | M | *FH* | Single syndrome-HLRCC | Papillary type II RCC | x | ✓ | x | x | NA | x |
| 49 | F | *FLCN* | Multi-gene panel[2] | Bilateral ccRCC<br>Spontaneous pneumothorax | x | ✓ | x | | | |
| NA | F | *VHL* | Single syndrome-VHL | CNS hemangioblastomas<br>Neuroendocrine tumor of pancreas / Reported VHL (no proof of testing available) | VHL | x | NA | x | NA | x |
| NA | F | *VHL* | Single syndrome-VHL Single syndrome-HBOC | Hemangioblastomas / Reported VHL (no proof of testing available) | VHL HBOC | x | NA | ✓ | NA | x |
| 60 | M | *BAP1* | Multi-gene panel | Bladder cancer, dx 60<br>ccRCC dx 67 Hx of polyposis<br>Melanoma dx 67<br>Lymphoma dx 67 | x | ✓ | x | x | NA | x |
| 25 | M | *SDHB* | Multi-gene panel | Oncocytoma type RCC dx 25<br>Loss of SDHB on IHC | x | ✓ | ✓ | x | NA | x |
| NA | F | *FLCN* | Single syndrome-BHD | Fibrofolliculomas / Pneumothoraces, fibrofolliculomas, pulmonary cysts | BHD | x | NA | x | NA | x |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 57 | F | *FLCN* | Multi-gene panel | RCC with mixed pathology (oncocytoma and papillary type) dx 57<br>Angiofibromas<br>Pulmonary cysts<br>Bilateral renal tumors<br>Spontaneous pneumothoraces | BHD | ✓ | x | x | NA | x |
| 39 | F | *TP53* | Multi-gene panel | ccRCC dx 39<br>Pancreatic cancer dx 52<br>LFS spectrum cancers | HBOC | ✓ | ✓ | x | NA | x |
| NA | F | *VHL* | Single syndrome-VHL | Hemangioblastomas<br>VHL (clinical and molecular dx) | VHL HBOC | x | NA | x | NA | x |
| 41 | M | *FLCN* | Single syndrome-BHD | Chromophobe RCC dx 41<br>Pulmonary cysts | x | ✓ | ✓ | x | NA | x |
| **Prostate-Related Referral Group** | | | | | | | | | | |
| 66 | M | *BRCA2* | Single site-familial mutation | Aggressive $PrCa_3$<br>Ovarian cancer | HBOC | ✓ | NA | x | ✓ | x |
| 47 | M | *BRCA2* | Single site-familial mutation | Aggressive PrCa<br>Three breast cancer primaries | HBOC | x | NA | x | ✓ | x |
| 68 | M | *BRCA2* | Single syndrome-HBOC | <br>Breast, ovarian cancer | HBOC | x | NA | x | ✓ | x |
| 53 | M | *BRCA2* | Single syndrome-HBOC | Aggressive PrCa<br>Breast cancer dx 41, 43 | HBOC | x | NA | x | ✓ | x |
| 67 | M | *ATM* | Single syndrome-HBOC + *ATM* | Aggressive PrCa<br>Breast cancer dx 31 | HBOC | x | NA | x | x | x |
| 55 | M | *BRCA2* | Multi-gene panel | Aggressive PrCa | x | x | NA | x | x | ✓ |
| 50 | M | *ATM* | Multi-gene panel | <br>Familial breast cancer | HBOC | x | NA | x | NA | ✓ |
| **Other Referrals** | | | | | | | | | | |
| 56 | F | *MSH2* | Single syndrome-HNPCC | UTUC dx 56<br>MSI-H, loss of *MSH2, PMS2* on IHC | x | ✓ | NA | x | NA | x |
| 67 | F | *FH* | Single syndrome HNPCC, Multi-gene panel | UTUC dx 67<br>MSI-H, loss of *MSH2, PMS2* on IHC<br>Paraganglioma of the bladder<br>Adrenal adenoma | x | x | NA | x | NA | x |
| 45 | F | *BRCA1* | Multi-gene panel | Breast cancer dx 45, 55<br>UTUC dx 70<br>Uterine cancer dx 70 | HBOC | x | NA | x | NA | x |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 54 | F | *MSH2* | Multi-gene panel | UTUC dx 54<br>MSI-H, loss of *MSH2, PMS2* on IHC | HBOC | ✓ | NA | x | NA | x |

**Appendix A**

Abbrieviations- Dx: diagnosis; mPrCa: metastatic prostate cancer; NA: not applicable; CNS: central nervous system; HLRCC: hereditary leiomyomatosis and RCC syndrome; BHD: Birt Hogg Dube syndrome; VHL: von Hippel Lindau disease; HBOC: hereditary breast and ovarian cancer syndrome; LFS: Li Fraumeni syndrome; UTUC: upper tract urothelial carcinoma; MSH-H: microsatellite high; IHC: immunohistochemistry staining

1 "Relatives" includes first, second, and third degree relatives only

2 See Appendix B for the genes included in all multi-gene panels

3 Aggressive prostate cancer defined by Gleason score ≥ 7

**Appendix B** Genes Included in Multi-Gene Panel Tests

| **Study ID** | **Panel Type** | **No. Genes on Panel** | **Genes Included** |
|---|---|---|---|
| 46, 118, 119 | RCC panel | 19 | *BAP1, EPCAM, FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHA, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL* |
| 97 | Pan-cancer panel | 49 | *APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP, CDH1, CDK, CDKN2A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, POLD1, POLE, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, BAP1, FH, FLCN, MAX, MEN1, MITF, MET, MRE11A, NF1, RAD50, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMARCA4, TMEM127, TSC1, TSC2, VHL* |
| 110 | PGL/PCC[1] syndrome panel | 5 | *SDHA, SDHB, SDHC, SDHD, SDHAF2* |
| 134 | Prostate panel | 12 | *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53* |
| 136 | PGL/PCC syndrome panel | 14 | *FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL, EGLN1, KIF1B* |
| 143, 215 | Custom panel | 12 | *BRCA1, BRCA2, ATM, PALB2, CHEK2, EPCAM, MLH1, MSH2, MSH6, PMS2, TP53, PTEN* |

| | | | |
|---|---|---|---|
| 157 | Prostate panel | 14 | *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53* |

**Appendix B**

[1]PGL/PCC: paraganglioma/ pheochromocytoma

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