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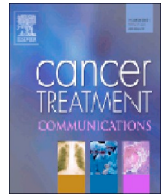
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Knowledge and practice regarding prostate cancer germline testing among urologists: Gaps to address for optimal implementation ☆,☆☆

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ABSTRACT

Background: Germline testing is recommended for all men with metastatic prostate cancer (PCa), and for some with localized PCa meeting specific histologic or family history criteria. Germline genetic evaluation has important implications for PCa prognosis and management, as well as implications for family members and cancer screening. Despite the importance of germline evaluation, its utilization in urologic practice is unknown.

Materials and Methods: We conducted a 32-item survey of U.S. urologists to examine knowledge of germline testing guidelines and practice patterns. It was shared through email to 6 American Urological Association sections, the Veterans Affairs Urology Mailgroup, and social media.

Results: Among 132 total respondents from diverse practice settings across the U.S., 12% perform germline testing, 44% refer to a genetic counselor, 11% do both, and 33% do not test/refer. Only 4% had formal education in genetics. While 98% ask about PCa family history, only 76% and 52% ask about breast and ovarian cancer. When presented with hypothetical case scenarios where germline testing is indicated, many respondents indicated they would not offer genetic counseling or testing. Younger age ($p = 0.03$), academic practice ($p = 0.04$), and specializing in PCa/oncology ($p = 0.007$) were significantly associated with performing or referring for germline testing. Specializing in PCa/oncology was significantly associated with recommending germline testing for all case scenarios involving metastatic PCa ($p = 0.0009$)

Conclusion: Our results suggest significant gaps in knowledge of germline testing and alignment of practice with national guidelines among urologists. Germline testing education and facilitation of genetic evaluation in urologic practice is warranted.

Clinical Practice Points

- Genetic testing has significant implications for patients with prostate cancer and their families.
- Broad family history collection is very important for optimal testing and genetic assessment.
- Genetic evaluation influences screening and treatment

decisions for prostate cancer.

Introduction

The past decade has witnessed rapid advances in genetic knowledge and precision medicine. Current guidelines recommend germline

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Table 1
Responses by urologists on germline testing for PCa patients*.

| Question | % |
|--|-----|
| Respondent Demographics and Practice Information | |
| Urologist Age (n = 128) | |
| ≤ 44 | 20% |
| 45–54 | 22% |
| 55–64 | 27% |
| ≥ 65 | 31% |
| Years in Practice (n = 126) | |
| 1–5 | 9% |
| 6–10 | 13% |
| 11–15 | 9% |
| 16–20 | 9% |
| 21–25 | 10% |
| 26–30 | 14% |
| ≥ 31 | 36% |
| Practice Setting (n = 127) | |
| Private | 45% |
| Academic | 39% |
| Private hospital | 16% |
| Public hospital | 6% |
| Veterans Affairs | 13% |
| Military | 0% |
| Community health center/HMO | 1% |
| Other | 4% |
| Primary Clinical Expertise (n = 126) | |
| Prostate Cancer | 10% |
| Urologic Oncology | 23% |
| General Urology | 58% |
| Other | 10% |
| How Often Seeing Patients with Advanced PCa (n = 132) | |
| Always | 16% |
| Often | 46% |
| Sometimes | 30% |
| Rarely | 8% |
| Never | 1% |
| Practice Results Regarding Family History Collection, Germline Testing and Management Implications | |
| Do you ask prostate cancer patients if other family members have had the following cancers (N = 131): | |
| Prostate Cancer | 98% |
| Breast Cancer | 76% |
| Ovarian Cancer | 52% |
| Colorectal Cancer | 48% |
| Pancreatic Cancer | 32% |
| Melanoma | 18% |
| Lung Cancer | 24% |
| Other Cancer | 16% |
| I don't ask about family members' cancer | 2% |
| If you ever recommend germline genetic testing, what do you test in men with PCa? | |
| I do not personally perform germline testing | 54% |
| BRCA1 and BRCA2 testing only | 3% |
| BRCA1, BRCA2 and ATM testing only | 6% |
| Premade prostate cancer specific panels | 7% |
| Large panel testing including homologous DNA repair | 4% |
| Large panel testing including homologous recombination and mismatch DNA repair | 9% |
| Not sure | 17% |
| Which of the following are important to discuss with patient prior to making an informed decision for genetic testing? (Check all that apply) (n = 129) (All are important to discuss) | |
| Cancer inheritance (i.e., how mutations are passed in families) | 58% |
| Risks, benefits, limitations of genetic testing | 66% |
| Types of genetic test results and implications for management | 43% |
| Genetic discrimination laws (GINA law) | 26% |
| Reproductive implications (i.e., possible conditions in future children if mutation) | 30% |
| Genetic testing of relatives (cascade testing) | 40% |
| None of the above | 2% |
| N/A- I do not perform testing | 23% |
| When do you recommend to start screening for men who are BRCA carriers? | |
| I do not recommend PCa screening | 4% |
| I recommend PCa screening starting before age 40 | 16% |
| I recommend PCa screening starting at age 40 | 52% |

Table 1 (continued)

| Question | % |
|---|-----|
| I recommend PCa screening starting at age 45 | 15% |
| I recommend PCa screening starting at age 50 | 5% |
| I recommend PCa screening starting at age 55 | 1% |
| Abstain | 6% |
| Other | 1% |
| Does the presence of a germline BRCA1, BRCA2 or ATM mutation in men with low-risk localized PCa influence your treatment decision? | |
| Yes, I do not recommend active surveillance | 27% |
| No, I discuss standard treatment options, including active surveillance | 42% |
| Abstain | 5% |
| Not qualified to answer | 26% |
| Does the presence of a germline BRCA1, BRCA2 or ATM mutation in men with intermediate or high-risk localized PCa influence your treatment decision? | |
| Yes I recommend radical prostatectomy over radiation therapy | 24% |
| Yes, recommend radiation therapy over radical prostatectomy | 2% |
| No, standard treatment recommendation | 48% |
| Abstain | 5% |
| Unqualified to answer | 21% |
| Does the presence of a DNA repair defect in men with newly-diagnosed metastatic castration-sensitive/naive prostate cancer influence your upfront treatment decision for men with metastatic disease? | |
| Yes, more likely to recommend Docetaxel to ADT | 12% |
| Yes, include Platinum in the chemo-hormonal therapy | 5% |
| Yes, other treatment recommendation | 12% |
| Abstain | 18% |
| Unqualified to answer | 54% |
| Knowledge of PCa Genetics and Risk Assessment | |
| Which of the following cancers may be connected to prostate cancer in families? (n = 131) (Correct answers) | |
| Breast Cancer (yes, through HBOC) | 92% |
| Ovarian Cancer (yes, through HBOC or Lynch syndrome) | 64% |
| Colorectal Cancer (yes, through Lynch syndrome) | 38% |
| Pancreatic Cancer (yes, through HBOC or Lynch syndrome) | 36% |
| Endometrial Cancer (Yes, through Lynch syndrome) | 17% |
| Lung Cancer (not connected to PCa) | 6% |
| Don't Know | 5% |
| Which of the following tests evaluate some genes linked with hereditary prostate cancer? (n = 130) (Correct answers) | |
| Prolaris (No) | 27% |
| Invitae Prostate Cancer Panel (Yes) | 30% |
| Color Hereditary Cancer Testing (Yes) | 27% |
| OncotypeDx (No) | 29% |
| Myriad Genetics myRisk Hereditary Cancer Test (Yes) | 58% |
| Decipher (No) | 20% |
| Don't Know | 16% |
| Which of the following genes have the strongest and consistent association to inherited prostate cancer risk? (Check all that apply) (n = 130) (Yes=Optimal choices) | |
| BRCA1 (Yes) | 62% |
| BRCA2 (Yes) | 78% |
| MLH, MSH2, PMS2, MSH6 (Lynch Syndrome Genes) | 26% |
| HOXB13 (Yes) | 25% |
| PALB2 | 8% |
| CHEK2 | 19% |
| NBN | 1% |
| TP53 | 13% |
| ATM | 25% |
| None of the above | 0% |
| Don't know | 19% |
| Which of the following genes are associated with aggressive or lethal prostate cancer? (n = 131) (Yes=Optimal Choice) | |
| BRCA1 | 49% |
| BRCA2 (Yes) | 63% |
| MLH, MSH2, PMS2, MSH6 (Lynch Syndrome Genes) | 19% |
| HOXB13 | 16% |
| PALB2 | 3% |
| CHEK2 | 13% |
| NBN | 0% |
| TP53 | 12% |
| ATM | 25% |
| None of the above | 1% |
| Don't know | 28% |

* Sample size for completed responses to each item is shown in the table. Unanswered items were not included in the calculation of percentages. Number

of blank answers per question ranged from 0 to 11 with a median of 4.

majority of participants see patients with advanced PCa sometimes (30%), often (46%) or always (16%).

Table 1 shows the results. Virtually all participants (98%) ask about family history of PCa, with most also obtaining information about relatives' age at diagnosis (93%), Gleason score (58%) and PCa death (95%). Although 76% of respondents ask about family history of breast cancer and 52% about ovarian cancer, a family history of other cancers was asked by less than half of respondents. Most respondents indicated interest in additional resources such as family history collection tools for patients or education updates, and 38% were interested in a smartphone app to refer patients for genetic evaluation.

Regarding germline testing, 12% perform germline testing in their practice, 44% refer to a genetic counselor, and 11% do both. Conversely, 33% do not perform testing or refer to a genetic counselor.

Respondents were presented with specific clinical scenarios in which germline testing is indicated and whether they would refer such a patient to a genetic counselor and/or perform testing (Table 2). A majority of urologist respondents would refer/test men with metastatic PCa with a family history of breast and ovarian cancer, or who have a BRCA mutation on tumor profiling. Fewer would refer/test patients with high-risk PCa who do not have a family history, or patients with low or very low-risk disease who meet criteria. Overall, only 2% of respondents answered correctly for all 11 case scenarios that are recommended in the NCCN guidelines. A total of 26% would refer or test for all 3 metastatic case scenarios, and 3% would refer or test for all 8 non-metastatic case scenarios.

In terms of additional barriers to optimal implementation, only 55% of respondents reported that they have access to a genetic counselor; however, a considerable proportion of urologists who perform germline testing do not discuss key topics such as genetic discrimination laws, reproductive implications, or testing of other relatives (Table 1). In the minority of participants who perform germline testing, there were mixed responses regarding the number of genes that should be tested (e.g. large panel versus PCa-specific panel versus BRCA1/2 and ATM testing only).

Urologists were asked how germline test results influence practice (Table 1). Only 30% of urologist respondents reported that germline results affect their PCa screening recommendations. The most common age to start screening was 40 for BRCA carriers (52%), while 16% recommend screening before age 40 in BRCA mutation carriers. Current

NCCN guidelines recommend starting PCa screening at age 40 for BRCA2 carriers and to consider the same for BRCA1 carriers [1]. For men with low-risk localized disease, 27% do include BRCA2 mutation results in active surveillance discussions, which is advocated in the NCCN Prostate Cancer guideline [2]. For newly diagnosed metastatic castration-sensitive PCa, most participants felt unqualified to answer whether DNA repair defects influence upfront management decisions.

Knowledge results. Regarding knowledge of germline testing for PCa, there was variability noted. Most urologist respondents are aware that breast cancer (92%) and ovarian cancer (64%) may be connected to PCa in families, but less than 40% were aware of a link to other cancers such as pancreatic, colorectal, or endometrial cancer suggestive of Lynch syndrome.

Although most urologists who responded to the survey use genomic tests in their practice (most commonly OncotypeDx, used by 60%), one-third were not confident in explaining genomic versus germline genetic testing. Approximately 25% of participants incorrectly indicated that genomic tests such as OncotypeDx and Prolaris evaluate some genes linked with hereditary cancer risk.

In terms of specific genes, 78% and 62% of respondents were aware of an association between BRCA2 and BRCA1, respectively, with inherited PCa risk; further, 63% of respondents reported an association between BRCA2 and aggressive or lethal PCa. A minority of respondents were aware of a link between HOXB13 with inherited PCa risk, where there is strong association.

Predictors of germline PCa testing. Table 3a and b show factors associated with the performance or consideration of germline PCa testing in urology practice. As shown in Table 3a, younger urologists ($p = 0.03$), those in academic practice ($p = 0.04$), and who specialize in PCa or oncology ($p = 0.007$) were significantly more likely to perform or refer patients for germline testing compared to those who did neither. Specializing in PCa or urologic oncology was significantly associated with recommending germline testing for all case scenarios from Table 2 involving patients with metastatic PCa ($p = 0.0009$) (Table 3b).

Discussion

Our nationwide survey of US urologists indicated a spectrum of practice regarding PCa germline testing, with nearly half referring to genetic counseling. A growing minority are performing germline PCa testing within their practices. However, gaps in family history

Table 2

Germline testing of men with prostate cancer based on specific clinical scenarios as indicated by NCCN guidelines) [1,2].*

| For each type of patient scenario below, please indicate if you perform or refer them for germline testing ($n = 120-126$): | Yes (refer or perform) | No | Don't assess |
|--|------------------------|-----|--------------|
| Guidelines: Testing is clinically indicated for metastatic prostate cancer at any age. | | | |
| Metastatic prostate cancer, mother with breast cancer, sister with ovarian cancer | 65% | 14% | 21% |
| Metastatic prostate cancer, no family history of malignancy | 31% | 44% | 25% |
| Metastatic prostate cancer, BRCA mutation in tumor profiling | 63% | 14% | 22% |
| Guideline: Germline testing is recommended for high-risk localized prostate cancer (T3a OR Grade Group 4 or 5, OR PSA > 20 ng/mL). | | | |
| High-risk localized prostate cancer (Gleason 10), no family history of malignancy | 40% | 39% | 21% |
| Guideline: Testing is clinically indicated for high-grade (Gleason score ≥ 7) prostate cancer with ≥ 1 close blood relative with metastatic prostate cancer at any age. | | | |
| High-risk localized prostate cancer (Gleason 10), brother died from prostate cancer | 68% | 19% | 14% |
| Guideline: Testing is clinically indicated for high-grade (Gleason score ≥ 7) prostate cancer with Ashkenazi Jewish ancestry. | | | |
| High-risk localized prostate cancer, Ashkenazi Jewish ancestry, no family history of malignancy | 50% | 28% | 21% |
| Intermediate-risk localized prostate cancer, Ashkenazi Jewish ancestry, no family history of malignancy | 28% | 45% | 27% |
| Low-risk prostate cancer, Ashkenazi Jewish ancestry, no family history of malignancy | 14% | 58% | 28% |
| Guideline: Testing is clinically indicated for individuals with a first or second degree blood relative with ≥ 1 close blood relative with breast, ovarian, pancreatic or high-grade (Gleason score ≥ 7) or intraductal prostate cancer at any age. | | | |
| Low-risk localized prostate cancer, mom and sister with breast cancer, maternal uncle with colorectal cancer | 58% | 23% | 19% |
| Guideline: Testing is clinically indicated for individuals with any blood relative with a known pathogenic variant in a cancer susceptibility gene. | | | |
| Low-risk prostate cancer, mom with BRCA mutation | 52% | 27% | 22% |
| Guideline: Testing is clinically indicated for intraductal prostate cancer at any age. | | | |
| Very low-risk localized prostate cancer with intraductal histology, no family history of malignancy | 12% | 60% | 27% |

* Each of these scenarios would meet current criteria for germline PCa testing.

Table 3
Utilization of germline testing/counseling (a) in general and (b) for patients with metastatic prostate cancer by demographic and practice characteristics.

| a) General utilization of germline testing/counseling | | |
|---|----------------------------|--------------|
| | % Urologists to Refer/Test | p-value |
| Age | | 0.03 |
| < 55 | 78% | |
| 55 + | 59% | |
| Years in Practice | | 0.07 |
| ≤ 25 | 76% | |
| > 25 | 61% | |
| Specialty in Urology | | 0.007 |
| Prostate Cancer/Oncology | 83% | |
| Other | 59% | |
| Practice Type | | 0.04 |
| Academic | 78% | |
| Other | 60% | |
| Frequency of Advanced PCa | | 0.45 |
| Often/Always | 69% | |
| Less Frequently | 63% | |

| b) Utilization of germline testing/counseling for patients with metastatic prostate cancer | | |
|--|-------------------------------|---------------|
| | % with All Metastatic Correct | p-value |
| Age | | 0.21 |
| < 55 | 31% | |
| 55 + | 22% | |
| Years in Practice | | 0.12 |
| ≤ 25 | 32% | |
| > 25 | 20% | |
| Specialty in Urology | | 0.0009 |
| Prostate Cancer/Oncology | 44% | |
| Other | 16% | |
| Practice Type | | 0.33 |
| Academic | 31% | |
| Other | 23% | |
| Frequency of Advanced PCa | | 0.96 |
| Often/Always | 26% | |
| Less Frequently | 25% | |

collection and knowledge were identified that need to be addressed for responsible implementation of PCa germline testing

To date, very few studies have examined family history data collection or use of genetic testing among urologists. A 2014 survey of 87 members of the Chicago Urological Society reported that 95% of urologists always obtained family history when discussing PCa risk and 87% when discussing screening options [11]. However, only 57% always obtained family history when discussing treatment options, primarily due to the belief that it would not change management. Our results show that while virtually all urologists collect data on family history of PCa, many do not ask about history of cancer in female relatives or other tumor types with genetic links to PCa. Broad family history collection is very important for optimal testing and genetic assessment, which encompasses genes linked with hereditary cancer syndromes.

A more recent survey of 52 large U.S. urology group practices reported that 63% were already offering testing to selected patients [12]. However, barriers to testing included concerns of medico-legal liability, reimbursement, and difficulty collecting detailed family history in the medical record. Our study expands upon these results by examining practice patterns in multiple practice settings and specific clinical scenarios. We found additional barriers in terms of specific knowledge gaps and preferences for additional resources, which are actionable results. In addition, we found that many urologists lack access to a genetic counselor, which might be improved in the future through the use of telemedicine or other technology-based solutions.

Finally, a 2017 survey of 691 providers reported that 26% of urologists and 4% of radiation oncologists frequently used "genetic

tests." [13] The most commonly employed tests were Prolaris and OncoType, neither of which captures germline genetic variants and are more appropriately classified as "genomic tests". Indeed, the use of genomic tests may be much more familiar in urologic practice compared to germline testing. In the 2019 American Urological Association census, 59% of U.S. urologists reported using genomic tests to help stratify patients with PCa for active surveillance, which corroborates our findings in this survey [7]. Despite the widespread use of genomic tests, more than 1/4 of respondents in our survey believed that the Prolaris, OncoType and/or Decipher tests evaluate genes linked with hereditary PCa. Our findings highlight the need for decision support tools or additional targeted education on PCa genetics, indications for germline testing and types of testing options.

In terms of screening recommendations, most urologists recommend screening starting at 40 for men with BRCA mutations. These are in line with current NCCN guidelines for Prostate Cancer Early Detection. Data from the IMPACT study suggested that targeted screening in BRCA mutation carriers detects a high proportion of clinically significant disease [14]. Similarly the American Urological Association Guidelines state that certain subgroups of men age 40 to 54 years may realize added benefit from earlier screening, including those with a family history of metastatic or lethal adenocarcinomas (e.g., prostate, male and female breast cancer, ovarian, pancreatic) spanning multiple generations, affecting multiple first-degree relatives, and that developed at younger ages.

With regard to PCa treatment, a minority of urologist respondents currently alter their management decisions based on germline results. For men with low-risk localized disease, 27% do not recommend active surveillance in the presence of a BRCA2 mutation. However, to date the main evidence on active surveillance is from a study by Carter et al. showing a significantly higher risk of grade reclassification among men with mutations in a 3 gene panel including BRCA1, BRCA2, and ATM [15]. Since these data are very early and based on a small sample size, it is possible that many urologists and/or patients do not find the strength of underlying evidence sufficient to alter practice patterns. Meanwhile, for men with intermediate or high-risk localized PCa, 24% would recommend prostatectomy over radiation therapy, despite no data in support of specific modalities of local therapy based on mutation status.

Compared to previous data from academic medical oncologists [6], the proportion of urologists who are comfortable performing germline testing is substantially lower. Possible reasons for these differences may include differential training and experience with germline testing in other patient contexts, and the extent to which germline results impact management decisions in advanced versus localized PCa. That notwithstanding, with most urologists reporting that they manage advanced PCa, and the 2020 American Urological Association guidelines recommend that clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. They also recommend offering pembrolizumab for patients with mismatch repair deficient or microsatellite instability high metastatic CRPC. Therefore, greater integration of genetic counseling models to facilitate germline testing into urological care is important at multiple points of patient care, in addition to implications for family members. Further qualitative research is warranted to define the barriers and facilitators to implementation of germline testing in urological practice. Future interventions should address urologists in the groups who are less likely to refer patients or perform testing (e.g., older age, non-academic, and those who do not specialize in PCa/oncology).

A limitation of the study is the low response rate, which is common in urological survey research [16]. According to the 2019 AUA census, there are 13,044 practicing urologists in the U.S. [7] At the time of distribution, the email and social media groups that we used to send out the survey included 13,363 total people; however not everyone on the

AUA section email lists is a practicing urologist eligible for the survey, and there is overlap between the AUA sections with the VA mailgroup and social media groups. Despite the use of several different distribution methods, our sample represents <1% of U.S. urologists. This limits the generalizability of our findings to the full landscape of urology practice in the U.S. Compared to data from the AUA census, our survey included fewer urologists with <25 years in practice (50% vs 59%), fewer in private practice (45% vs 53%), and specializing in general urology (58% vs 60%). Additional demographic data for providers (e.g., gender and race/ethnicity) were not asked in the survey. Also, responses about the frequency of seeing patients with metastatic prostate cancer are subjective and we do not have objective clinical data to examine this or utilization of precision therapy in clinical practice.

Another limitation of the study is that the reported percent of urologists who perform germline testing may be an overestimate, since approximately 1/3 of respondents were uncertain about the difference between genomic versus germline testing. In addition, our survey did not ask about additional potential barriers to germline testing (e.g., reimbursement issues, organizational factors) that might influence testing patterns. Also, there is some variability in guidelines across NCCN panels and some of the testing criteria are based on expert opinion, which may have influenced responses to the case scenarios. Additional qualitative work is important to follow up on these findings and explore the factors that influence uptake of genetic evaluation in practice.

Strengths of our study include sampling from a geographically diverse sample of urologists from diverse practice settings across the U.S. Our study included very detailed information on family history collection and case-based use of germline testing, which provide an important snapshot into current patterns of care with respect to germline genetic evaluation in urological practice. On the basis of participant responses, several key gaps or barriers were identified with proposed solutions to better operationalize PCa germline testing in urology practice. These data highlight numerous gaps for future research (e.g., barriers and facilitators to germline genetic evaluation) as well as actionable findings to promote guideline-concordant care, including new opportunities for continuing education for urologists about genetic risk assessment and decision support tools to aid in clinical decision-making regarding germline evaluation.

Conclusions

Given the substantial implications of genetic testing for patients and their families, it is essential that urologists have the education and practice resources to responsibly implement genetic assessment in clinical practice. Although most urologists manage patients with advanced PCa, 1/3 of urologists neither refer patients to genetic counseling nor perform germline testing in their practice. Our survey has identified numerous actionable gaps, which will inform future research on how to optimize the implementation of genetic evaluation into urological care.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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