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Germline Pathogenic Variants Identified in Patients With Genitourinary Malignancies Undergoing Universal Testing: A Multisite Single-Institution Prospective Study

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Study Need and Importance: Identifying pathogenic germline variants (PGVs) in genitourinary (GU) cancer patients can have important implications for treatment decisions, cancer screening, and germline testing for close relatives. This study aimed to investigate the prevalence of PGVs in hereditary cancer genes utilizing a universal testing approach and to determine the rate of PGVs that would have been missed based on NCCN (National Comprehensive Cancer Network) guidelines in GU malignancies.

What We Found: A multisite, single-institution prospective germline genetic test (GGT) was universally offered to patients with new or active diagnoses of GU malignancies. More than 1 in 8 patients with GU malignancies were found to carry a PGV (Figure), with 67% of patients with high-penetrance PGVs undergoing clinically actionable changes. PGV-positive patients who would not have received testing based on NCCN guidelines were identified in 28 (57%) prostate, 15 (100%) bladder, and 14 (78%) renal cancer patients.

Limitations: The limitations of our study include the relatively short follow-up period and small sample size. In addition, there are limitations to the generalizability of the study, given all patients were seeking care at a tertiary care center.

Interpretation for Patient Care: These findings support universal GGT for GU malignancies and underscore its potential to enhance risk assessment and guide precision interventions in urologic oncology. Our study contributes to the expanding body of evidence supporting the importance of considering PGV in traditional high-risk scenarios and across a broader spectrum of patients affected by GU cancers. As novel therapeutic strategies emerge that target specific genetic vulnerabilities, our study reinforces the necessity of broad-based GGT to identify these susceptibilities and optimize treatment approaches in urologic oncology.

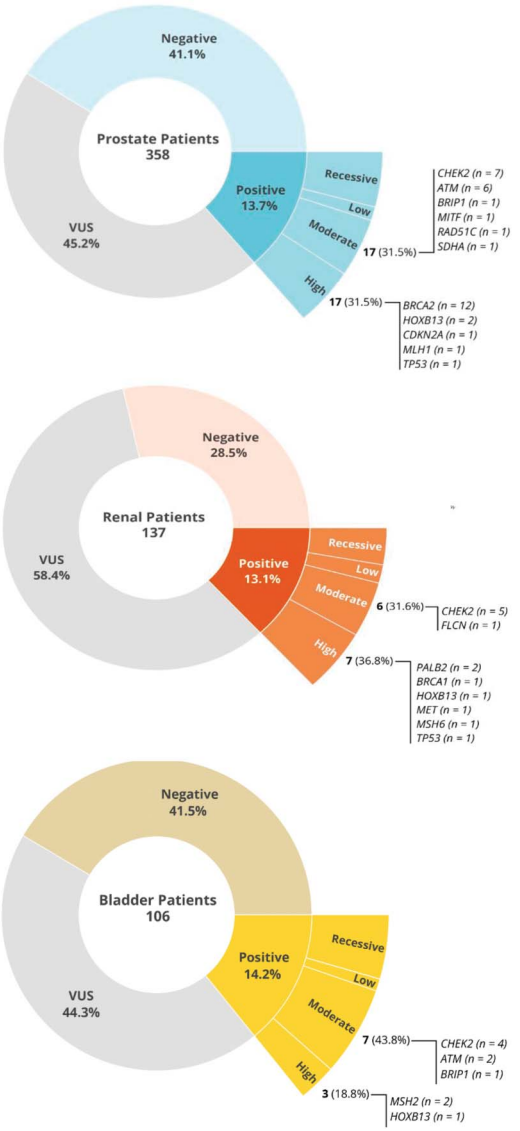

Figure. Distribution of germline testing results for prostate patients (A), renal patients (B), and bladder patients (C). VUS indicates variants of uncertain significance.

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Germline Pathogenic Variants Identified in Patients With Genitourinary Malignancies Undergoing Universal Testing: A Multisite Single-Institution Prospective Study

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Purpose: This study aimed to investigate the prevalence of pathogenic germline variants (PGVs) in hereditary cancer genes utilizing a universal testing approach and to determine the rate of PGVs that would have been missed based on National Comprehensive Cancer Network (NCCN) guidelines in genitourinary (GU) malignancies.

Materials and Methods: A multisite, single-institution prospective germline genetic test (GGT) was universally offered to patients with new or active diagnoses of GU malignancies (prostate, bladder, and renal) from April 2018 to March 2020 at Mayo Clinic sites. Participants were offered GGT using a next-generation sequencing panel of $>$ 80 genes. Demographic, tumor characteristics, and genetic results were evaluated. NCCN GU cancer guidelines were used to identify whether patients had incremental findings, defined as PGV-positive patients who would not have received testing based on NCCN guidelines.

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Conflict of Interest Disclosures: Dr Samadder has been a consultant for Recursion Pharmaceuticals, One-Two Therapeutics, and Jansen Research and Development. Drs Esplin, Nielsen, BH, and RLN are employees and stockholders of Invitae.

Ethics Statement: This study received Institutional Review Board approval (IRB No. 18-00326). This submission and all authors complied with the FAIR principles (Findability, Accessibility, Interoperability, Reproducibility). Informed consent was obtained from each participant of the study.

Author Contributions:

Conception and design: Kunze, Nielsen, Esplin, Andrews, Samadder.

Data analysis and interpretation: Durant, Choudry, Warren, Kunze, Golafshar, Nielsen, Esplin, Andrews, Tyson.

Data acquisition: Durant, Choudry, Edmonds, Warren, Kunze, Nielsen.

Drafting the manuscript: Durant, Choudry, Edmonds, Warren, Kunze, Golafshar, Esplin.

Critical revision of the manuscript for scientific and factual content: Choudry, Warren, Kunze, Golafshar, Nielsen, Esplin, Andrews, Samadder, Tyson.

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Results: Of 3095 individuals enrolled in the study, 601 patients had GU cancer (prostate = 358, bladder = 106, and renal = 137). The mean enrollment age was 67 years (SD 9.1), 89% were male, and 86% of patients were non-Hispanic White. PGVs were identified in 82 (14%) of all GU patients. PGV prevalence breakdown by cancer type was: 14% prostate, 14% bladder, and 13% renal cancer. Nearly one-third of identified PGVs were high penetrance, and the majority of these (67%) were clinically actionable. Incremental PGVs were identified in 28 (57%) prostate, 15 (100%) bladder, and 14 (78%) renal cancer patients. Of the 82 patients with PGV findings, 29 (35%) had at least 1 relative undergo cascade testing for the familial variant(s) identified.

Conclusions: More than 1 in 8 patients with GU malignancies were found to carry a PGV, with 67% of patients with high-penetrance PGVs undergoing clinically actionable changes. The majority of these PGVs would not have been identified based on current testing criteria. These findings support universal GGT for GU malignancies and underscore its potential to enhance risk assessment and guide precision interventions in urologic oncology.

Urologic cancers account for approximately 10% of all cancer deaths in the US, with an estimated new 288,300 prostate, 82,290 bladder, and 81,800 renal cases in 2023 alone.[1,2] Previous studies have shown that inherited genetic variants (pathogenic germline variants [PGVs]) can significantly increase the risk for prostate, bladder, and renal cell cancer.[3-6] Identification of a germline predisposition in affected patients can have important implications for treatment decisions, risk-reducing interventions, cancer screening, and germline testing for their close relatives.[7] In recent years, there has been an exponential rise in understanding the role of PGV in genitourinary (GU) cancer predisposition and the development of new targeted therapies. However, germline genetic testing (GGT) guidelines for most GU malignancies remain unclear (bladder, renal) or complex and highly restrictive (localized prostate).[8]

Eligibility for GGT has traditionally been based on pathologic features of the cancer, age at diagnosis, family history of cancer, and other factors stipulated in clinical practice guidelines.[9] Currently, guidelines for patients with prostate cancer only recommend GGT for those with a strong family history, high-/very-high–risk disease, metastatic disease, and those with a personal history of breast cancer or Ashkenazi Jewish ancestry.[10] For bladder cancer, guidelines recommend GGT for patients with stage 3b disease and above, and for those with upper tract urothelial carcinoma (UTUC) who have a high probability of Lynch syndrome–related cancers.[11] Lastly, for renal cancer, patients under 46 years of age, those with multifocal masses, or first- or second-degree relatives with renal carcinoma are recommended to undergo genetic evaluation. Studies have primarily been retrospective cohorts of convenience from genetic testing laboratories, high-risk cancer clinics, or biobanks of patients with advanced disease, and thus are prone to referral and ascertainment bias.[12-14] Furthermore, outside of the PROCLAIM trial,[15] no studies have prospectively evaluated the clinical outcomes of universal, multigene panel genetic testing in patients with GU cancers compared with guideline-concordant selection for GGT. The advent and now Food and Drug Administration approval of PARP inhibitors in men with germline DNA damage response mutations and metastatic prostate cancer highlights the importance of understanding and characterizing the prevalence of PGVs in all urologic malignancies.

In this context, we report the clinical characteristics and results of a multisite prospective cohort of patients with GU malignancies who underwent GGT with an 80+ gene multicancer panel. This prospective study aimed to characterize the prevalence of PGVs with universal testing, explore differences in patient characteristics and outcomes, and assess the capture rate of PGVs with current guideline screening recommendations for prostate, bladder, and renal cancers.

METHODS

Patient Selection

The INTERCEPT study was approved by the Mayo Clinic Institutional Review Board (18-000326). A multisite single-institution prospective germline genetics evaluation was performed among patients with new or active diagnoses.[1] GU malignancy patients (prostate, renal, and bladder cancers including UTUC) were enrolled from April 1, 2018, to March 31, 2020. Radiation oncologists, medical oncologists, and urologists enrolled patients at the following participating care centers: Mayo Clinic Cancer Centers in Rochester, Minnesota; Jacksonville, Florida; Phoenix, Arizona; and Mayo Clinic Health System, Eau Claire, Wisconsin. Patients of all stages, races/ethnicities, familial history, and age were included in the study. At no cost, participants completed GGT using a next generation sequencing panel of 83 genes (84 genes as of July 2019) on the Invitae® Multi-Cancer Panel. Each patient was assessed for eligibility based on GGT guidelines for the National Comprehensive Cancer Network (NCCN), the National Society of Genetic Counselors (NSGC), or the American College of Medical Genetics (ACMG) for their specific cancer. Results were then reviewed with the patient by either the genetic counselor or physician involved in oncologic care. Clinical, demographic, pathologic, and family history data were collected and de-identified for reporting. Retrospective

chart review was conducted (November 2023) to determine if any clinical management or treatment changes were made based on genetic counseling for the PGV findings.

Sequencing, Variant Calling, and Result Reporting

As previously described, full gene sequencing, deletion/duplication analysis, and variant interpretation were performed at Invitae (San Francisco, California).[1-3] Germline variants were classified as no pathogenic variants identified, variants of unknown significance (VUS), or pathogenic/likely pathogenic (PGV). An incremental finding was defined as either a patient who would not have received testing based on NCCN/NSGC/ACMG guidelines or a patient with a PGV that fell outside the recommended testing panel for their cancer diagnosis. PGVs were categorized by penetrance level: high (>50% lifetime risk of cancer), moderate (20%-50% lifetime cancer risk), or low/undefined (undefined or <20% lifetime cancer risk). Carriers were defined as individuals with a single PGV identified in a gene associated with autosomal recessive inheritance.

Cascade testing for the familial variant was offered at no cost to all blood relatives of individuals with any PGV within a 150-day window of the patient's finalized test result report. The number of probands with at least 1 relative undergoing cascade testing and the total number of relatives undergoing cascade testing per proband were counted.

Statistical Analysis

Descriptive statistics were used to assess demographic and clinical characteristics of the 3 cohorts. We report rates of PGVs observed in each cohort. We compared categorical variables for group differences of interest using Pearson χ^2 tests and continuous variables using analysis of variance. We calculated rates of incremental findings for each cancer cohort. Additionally, for PGVs, low, moderate, and high penetrance rates were calculated. Percentages were calculated using only cases where data were present. $P < .05$ was considered to be statistically significant.

RESULTS

Cohort Characteristics

From April 1, 2018, through March 31, 2020, 3095 patients were enrolled in the INTERCEPT study.[1] A total of 601 patients had cancer of GU origin: prostate cancer 358, renal cancer 137, and bladder cancer 106 patients. The demographic and clinical characteristics of these patients are reported in Table 1. Most patients were male (89%) and non-Hispanic White (86%); the median age of enrollment was 68 years. Family history of cancer was reported in 321 (55%) patients. Values for individual cohorts are reported in Supplementary Tables 1-3 (https://www.jurology.com).

Variant Detection and Association With Clinical Characteristics

A total of 89 PGVs were identified in 82 patients (14%), and VUS, in the absence of PGV, were identified in 289 (48%) patients. PGVs were identified in 14% prostate, 13% renal, and 14% bladder cancer patients. VUS-only results were identified in 45% prostate, 58% renal, and 44% bladder cancer patients. PGVs were stratified into high (n = 27), moderate (n = 30), low/uncertain (n = 7), and carrier (n = 25) risk categories (Figure). The most frequent PGVs were in the following genes: *CHEK2* (n = 16, 18%), *MUTYH* carriers (n = 14, 16%), and *BRCA2* (n = 12, 14%). Seven patients were found to have 2 PGVs. Nearly one-third (27 of 89, 30%) of identified PGVs were in high-penetrance genes. PGVs consisted of 42 (47%) copy number variations and 47 (53%) missense variants. The distribution of GGT results and PGV genes varied by malignancy type (Figure). Supplementary Tables 1-3 (https://www.jurology.com) include demographic and clinical characteristics by GU cancer type and revealed no factors that were significantly associated with PGVs beyond a history of familial hereditary cancer syndromes.

Application of Clinical Genetic Referral Criteria

Amongst the 82 patients identified with PGV, 57 (70%) would have been missed based on 2020 NCCN/NSGC/ACMG guidelines.[16-19] The distribution of incremental findings by GU cancer type is described in Table 2. Incremental findings were identified in 57% (n = 28), 78% (n = 14), and 100% (n = 15) of prostate, renal, and bladder cancer patients, respectively.

Changes in Clinic Management Recommendations

Of the 27 high-penetrance PGVs, 67% (n = 18) had clinical management or treatment changes based on their GGT results. Most commonly, more frequent surveillance exams, imaging, or testing was recommended (n = 13). Targeted therapy was implemented for 5 patients with a high-penetrance PGV, and a change in surgical management occurred in 3 patients based on PGVs (Supplementary Table 4, https://www.jurology.com).

Cascade Testing Uptake

Of the 82 patients with positive or carrier results, 29 (35%) had > 1 relative who underwent testing for the familial variant(s) at the laboratory where the proband was tested. A total of 75 relatives underwent testing (range, 1-12 relatives per proband), with the majority of probands having only 1 (45%) or 2 (28%) blood relatives tested. Of the 75 family members who underwent cascade testing, 39 (52%) had at least 1 PGV or carrier finding identified.

Table 1. *Clinical and Demographic Characteristics of Included Patients*

	Prostate (N = 358)		Renal (N = 137)		Bladder (N = 106)	
Germline result, No. (%)						
Positive	49	(14)	18	(13)	15	(14)
Negative	147	(41)	39	(29)	44	(42)
VUS	162	(45)	80	(58)	47	(44)
Enrollment region, No. (%)						
Midwest	17	(5.0)	7	(5.1)	6	(6.0)
Southeast	77	(22)	43	(31)	32	(30)
Southwest	264	(74)	87	(64)	68	(64)
Gender, No. (%)						
Male	358	(100)	99	(72)	78	(74)
Female	0	(0.0)	38	(28)	28	(26)
Age, y						
Median (Q1, Q3)	69	(64, 74)	63	(56, 70)	69	(63, 74)
Race, No. (%)						
White	301	(84)	114	(83)	101	(95)
Non-White	57	(16)	23	(17)	5	(5.0)
Ethnicity, No. (%)						
Hispanic/Latino	21	(5.9)	11	(8.0)	3	(2.8)
Non-Hispanic	337	(94)	126	(92)	103	(97)
History of smoking?, No. (%)						
Yes	160	(45)	51	(38)	57	(55)
Missing	4		2		2	
Alcohol use, No. (%)						
Yes	108	(31)	34	(25)	25	(24)
Missing	11		2		3	
Obesity (BMI >30; at time of consent), No. (%)						
Yes	116	(33)	51	(38)	32	(31)
Missing	2		2		2	
Diabetes mellitus (at time of consent), No. (%)						
Yes	78	(22)	23	(17)	16	(15)
Missing	3		2		2	
Hypertension (at time of consent), No. (%)						
Yes	180	(51)	76	(56)	56	(54)
Missing	3		2		2	
Prior history of cancer, No. (%)						
Yes	23	(6.5)	19	(14.1)	9	(8.7)
Missing	5		2		2	
What type of prior cancer?, No. (%)						
Breast	0	(0.0)	5	(28)	1	(11)
CNS	0	(0.0)	1	(5.6)	0	(0.0)
GI	2	(9.5)	1	(5.6)	1	(11)
GU	9	(43)	6	(33)	7	(78)
Head and neck	4	(19)	2	(11)	0	(0.0)
Lung	2	(9.5)	0	(0.0)	0	(0.0)
Melanoma	3	(14)	2	(11)	0	(0.0)
Sarcoma	1	(4.8)	1	(5.6)	0	(0.0)
Family history of cancer, No. (%)						
Yes	181	(53)	76	(57)	64	(63)
No	155	(45)	51	(38)	33	(33)
Unknown	9	(2.6)	7	(5.2)	4	(4.0)
Missing	13		3		5	
Family history of hereditary cancer syndrome, No. (%)						
Yes	5	(1.5)	2	(1.6)	1	(1.0)
Missing	15		9		9	
Overall stage or prognostic group, No. (%)						
0	0	(0.0)	0	(0.0)	1	(1.0)
I	71	(21)	40	(31)	23	(23)
II	67	(20)	9	(7.0)	29	(29)
III	86	(25)	35	(27)	22	(22)
IV	114	(34)	45	(35)	24	(24)
Missing	20		8		7	
Recurrence or progression, No. (%)						
Yes	210	(61)	78	(60)	59	(60)
Missing	14		7		7	
Surgical resection for the indicated primary cancer site?, No. (%)						
Yes	146	(48)	113	(88)	86	(90)
Missing	52		8		10	
Radiation for the indicated primary cancer site?, No. (%)						
Yes	199	(64)	10	(9.0)	14	(17)
Missing	46		19		21	

(continued)

Table 1. (*continued*)

	Prostate (N = 358)	Renal (N = 137)	Bladder (N = 106)
Chemotherapy for the indicated primary cancer site?, No. (%)			
Yes	219 (66)	36 (29)	78 (77)
Missing	25	12	5
Immunotherapy for the indicated primary cancer site?, No. (%)			
Yes	23 (8.0)	65 (54)	52 (57)
Missing	69	17	14
CCI Score			
Mean (SD)	7.6 (2.6)	7.5 (3.0)	8.1 (2.7)
Median (Q1, Q3)	8.0 (5.0, 9.0)	8.0 (5.0, 9.0)	9.0 (6.0, 10)
Range	1.0-13	0.0-18	2.0-13
Is the patient deceased?, No. (%)			
Yes	77 (22)	42 (32)	32 (31)
Missing	11	5	3

Abbreviations: CCI, Charlson Comorbidity Index; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; VUS, variants of uncertain significance.
Percentages calculated by column.

DISCUSSION

In this study, the prevalence of pathogenic germline variants in GU malignancies underscores their emerging significance in the landscape of urologic oncology. Our findings reveal a noteworthy prevalence of PGVs across prostate (14%), bladder (14%), and renal (13%) cancers aligning with prior evidence that PGVs can substantially elevate the risk for these malignancies.[20,21] This emphasizes the previously underestimated role of germline predisposition in the context of urologic cancers. The observed prevalence rates in our study further substantiate the growing recognition of the complex interplay between genetic susceptibility and tumor development in GU malignancies. Our study contributes to the expanding body of evidence supporting the importance of considering PGV in traditional high-risk scenarios and across a broader spectrum of patients affected by GU cancers. As novel therapeutic strategies emerge that target specific genetic vulnerabilities, our study reinforces the necessity of broad-based GGT to identify these susceptibilities and optimize treatment approaches in urologic oncology.

Comparing our study outcomes with the existing NCCN/NSGC/ACMG guidelines for GGT in GU cancers reveals a critical area for reconsideration and refinement. The observed prevalence of PGVs that would have been missed based on these guidelines underlines the limitations of the current criteria in capturing the full spectrum of genetic susceptibilities. Notably, a substantial proportion of patients harboring PGV did not fit the traditional criteria for GGT, indicating that the conventional guideline-concordant approach might inadvertently exclude individuals who could benefit from early detection, tailored interventions, and informed counseling. This calls for reevaluating the criteria for genetic testing in urologic malignancies to ensure that patients with relevant germline variants are not overlooked. The data presented here provide compelling evidence to prompt discussions among clinicians, genetic counselors, and stakeholders in urologic oncology to formulate more inclusive and effective guidelines that encompass the broad range of hereditary cancer disorders identified through universal germline testing approaches. Such an evolution in genetic testing practices has the potential to substantially enhance patient care and outcomes in the GU cancer landscape.

Regarding prostate cancer, it is well established that PGVs occur in 1% to 5% of localized and 10% to 20% of metastatic patients.[4-8] This has translated to NCCN guidelines recommending GGT based on the presence of high-risk localized prostate cancer, metastatic disease, or significant familial history.[9] Yet, the present study reveals nearly 10% of stage 1 patients (7/71 patients) enrolled in the study were found to have PGV. The question remains whether these guidelines require updating to reduce actionable variants missed, especially given advancements in targeted therapies for prostate cancer.[11,12] Nicolosi et al[5] previously performed a cross-sectional study of 3607 men with prostate cancer who underwent germline genetic testing. Of these patients, up to 37% of those with positive genetic variants would not have met NCCN criteria for germline genetic testing.[5] More recently, the PROCLAIM trial enrolled 958 prostate cancer patients from 2019 to 2021 in the US and revealed current NCCN guidelines would have overlooked nearly half of prostate cancer patients with PGV.[15] These studies, along with the currently presented data, contribute to a growing discussion on the number of patients with missed PGV based on restrictive germline testing and suggest that germline testing recommendations should be reevaluated.[22]

Similarly, we propose an expansion of GGT guidelines for urothelial malignancies. Currently,

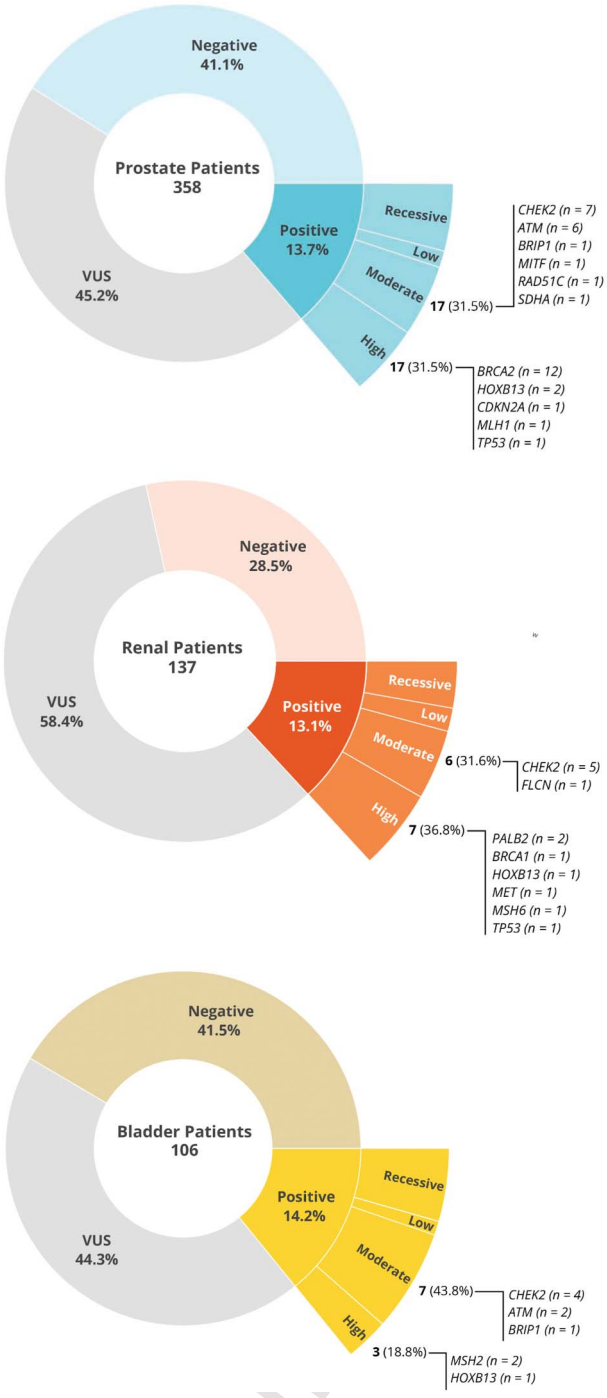

Figure. Distribution of germline testing results for prostate patients (A), renal patients (B), and bladder patients (C). VUS indicates variants of uncertain significance.

as mentioned previously, guidelines recommend GGT for patients with stage 3b disease and above and for those with UTUC who have a high probability of Lynch syndrome–related cancers. Only molecular somatic genomic testing for *FGFR3* or *FGFR2* genetic alterations are suggested for locally advanced or metastatic urothelial disease due to the potential use of erdafitinib, but there is no reference to GGT.[13] Mossanen et al[23] showed that familial bladder cancer accounted for 4.3% of bladder cancer cases, with the most frequently detected variants being *MSH2*, *BRCA1*, and *MLH1*. In our study we found that 2 patients within the bladder cancer cohort were found to have *MSH2* variants and eventually diagnosed with Lynch syndrome following guideline-discordant universal GGT. Yap et al[14] determined the prevalence of PGVs in malignancies without standard recommendations for genetic evaluation or testing and argued for the evolution of bladder cancer guidelines as PGVs were identified in 6.6% (79/1188) of the bladder cancer patients. However, which patients should be offered testing remains controversial. As expected, muscle-invasive bladder cancer has been associated with a > 2-fold increase in PGV.[24] Nevertheless, Pietzak et al[25] revealed even in high-risk nonmuscle-invasive bladder cancer, rates of PGV are as high as 14% of patients. Nearly 15% of bladder cancer patients in the present study had a PGV, emphasizing the need for further research in optimizing GGT guidelines in urothelial malignancies.

Renal cancer patients are screened for renal cell carcinoma (RCC) predominant hereditary syndromes based on a diagnosis of < 46 years of age, multifocal tumors, or a significant family history.[17] Yet, multiple studies have argued that advanced RCC alone should be considered a criterion for GGT.[26,27] Of stage 3 and 4 RCC patients, 16% were found to have a PGV in a cohort study conducted at Memorial Sloan Kettering Cancer Center.[17] Another study that evaluated PGV prevalence regardless of stage identified over 6% of RCC patients possessed a PGV.[27] Correspondingly, the present study identified 13% of all renal cancer patients (18/137 patients) had a PGV, and of stage 1 patients, 7.5% of patients had a PGV (3/40 patients).

Determining presence of a PGV is critical as they have the potential for therapeutic opportunities. For example, *BRCA2*-targeted therapies have been shown to be particularly successful among metastatic prostate cancer patients.[11,12,28] In our analysis, PGVs in *BRCA2* were the most common finding (n = 12, 22%) in patients with prostate cancer, as expected.[4,5] All *BRCA2*-positive patients within the study had clinically actionable change as a result of the PGV findings as they required more frequent surveillance exams, and 5 patients subsequently pursued targeted therapy. Interestingly, *CHEK2* (n = 4, 25%) was the most frequent PGV in bladder cancer as opposed to *MSH2*, which has been reported in other germline analyses of high-risk urothelial carcinoma.[29,30] *CHEK2* was the most common PGV in renal malignancies (n = 5, 26%), a finding in line with various other RCC studies[26,27,31] and reflective of a well-described association of

Table 2. *2020 National Comprehensive Cancer Network/National Society of Genetic Counselors/American College of Medical Genetics Criteria Performance in Patients With Pathogenic Germline Variants*

	Prostate (N = 49)	Renal (N = 18)	Bladder (N = 15)
Did they meet NCCN/NSGC/ACMG testing guidelines for their primary cancer?, No. (%)			
Yes	35 (71)	11 (61)	3 (20)
No	14 (29)	7 (39)	12 (80)
Did they meet guidelines based on family history regardless of personal history?, No. (%)			
Yes	20 (41)	5 (28)	5 (33)
No	22 (45)	12 (67)	5 (33)
Not available	7 (14)	1 (6.0)	5 (33)
Was PGV outside of the primary genes recommended for their primary cancer?, No. (%)			
Yes	21 (43)	12 (67)	12 (80)
No	26 (53)	4 (22)	3 (20)
Preliminary evidence	2 (4.1)	2 (11)	0 (0.0)
Incremental finding, No. (%)			
Yes	28 (57)	14 (78)	15 (100)
No	21 (43)	4 (22)	0 (0.0)

Abbreviations: ACMG, American College of Medical Genetics; NCCN, National Comprehensive Cancer Network; NSGC, National Society of Genetic Counselors; PGV, pathogenic variants.

CHEK2 with RCC in the literature.[32-34] RCC cohorts restricted to patients with early-onset (<46 years of age) disease were more likely to harbor PGVs in genes associated with hereditary RCC syndromes (eg, VHL, FH, SDHB).[32] Though our study did not evaluate PGV in testicular cancer, studies performed by Pyle et al[35] showed that *CHEK2* was also the most common variants identified in men with testicular germ cell tumor. Growing evidence exists that GGT guidelines frequently miss large proportions of PGVs across multiple cancer disease groups; this study highlights this observation in urologic malignancies.[1]

Cascade familial variant testing (FVT) in disease-free relatives affords the opportunity for genetically targeted primary disease prevention.[36,37] In our cohort, the overall rate of cascade testing was 35%, aligning with a growing body of research on the uptake of family testing for hereditary cancers.[1,38,39] Previous studies have consistently shown a generally low uptake in cascade family testing. Among the overall INTERCEPT cohort, 18% with PGVs had relatives who underwent FVT within a 3-month window of their test result.[1] Notably, cascade testing was even as low as 1.5% amongst blood relatives of those with hepatobiliary cancers.[40] A variety of factors can be contributing to this low uptake including limited understanding of genetic testing, communication barriers, financial constraints, and fear of discrimination or subsequent medical procedures.[41] Increased implementation of educational materials such as websites, videos, letters, and brochures could help with some of those barriers and lead to increased uptake of cascade FVT. Furthermore, these data highlight the need for future studies to delve deeper into understanding the motivations and barriers that individuals encounter when contemplating genetic testing.[42]

Several limitations of our study warrant consideration in interpreting the findings. First, the sample size and composition may introduce inherent biases, limiting the generalizability of the results to broader populations. The patient cohort primarily consisted of individuals seeking care at Mayo Clinic centers, potentially influencing the observed prevalence of germline variants. Moreover, the study's retrospective nature and relatively short follow-up duration hinder a comprehensive assessment of long-term clinical outcomes associated with specific germline variants. While our study provides valuable insights into the incremental yield of universal GGT, the absence of a randomized control group following guideline-concordant testing prevents direct comparison of clinical outcomes between testing strategies.

Looking ahead, several avenues for future research emerge from our study. In-depth functional studies of the identified PGVs can elucidate the precise mechanisms through which these genetic alterations contribute to tumor initiation and progression. Integrating genomic data with clinical outcomes on a larger scale could provide a more comprehensive understanding of the prognostic significance of specific variants. Prospective studies with extended follow-up periods are essential to assess the long-term impact of germline variant status on patient survival and treatment responses. Additionally, investigations into the cost-effectiveness of universal GGT compared to guideline-concordant testing can guide health care policies and resource allocation. As of 2022, the NCCN colon cancer guidelines recommend all patients undergo GGT.[43] However, a paucity of data exists on the financial toxicity of these recommendations. For GU cancers the question remains, and there is a need for future work assessing the cost burden of GGT in patients. Not only are cost considerations necessary for patients, but psychosocial

implications must be weighed. It is well established that genetic testing can lead to psychological distress for patients.[44] If universal GGT was accepted for GU oncology patients, this would call for the implementation of appropriate psychosocial support and medical education to help patients navigate GGT results. As the field of GU oncology continues to evolve, collaborative efforts are required to validate and expand upon the findings presented in this study, ultimately enhancing the precision of patient care and advancing the integration of genetic insights into routine clinical practice.

CONCLUSIONS

In conclusion, our multisite, single-center study unveils the substantial prevalence of germline variants in GU malignancies, challenging conventional notions of genetic testing criteria. Identifying pathogenic germline variants in over one-tenth of patients across prostate, renal, and bladder cancers underscores their integral role in the landscape of urologic oncology. Our findings advocate for a broader perspective on genetic testing, encouraging the adoption of universal testing approaches that transcend traditional clinical parameters.

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