Implementation of Universal Germline Genetic Testing Into Standard of Care for Patients With Prostate Cancer: The Time Is Now

Neal Shore, MD[1]; Sarah M. Nielsen, MS[2]; Edward D. Esplin, MD, PhD[2]; Emmanuel S. Antonarakis, MD[3]; Pedro C. Barata, MD[4]; Tomasz M. Beer, MD[5,6]; Himisha Beltran, MD[7]; Alan Bryce, MD[8]; Michael S. Cookson, MD[9]; E. David Crawford, MD[10]; Tanya B. Dorff, MD[8]; Daniel J. George, MD[11]; Elisabeth I. Heath, MD[12]; Brian T. Helfand, MD, PhD[13]; Maha Hussain, MD[14]; Rana R. Mckay, MD[10]; Alicia K. Morgans, MD, MPH[7]; Michael J. Morris, MD[15]; Channing J. Paller, MD[16]; Ashley E. Ross, MD, PhD[14]; Oliver Sartor, MD[17]; John Shen, MD[18]; Paul Sieber, MD[19]; Matthew R. Smith, MD, PhD[20]; David R. Wise, MD, PhD[21]; and Andrew J. Armstrong, MD[11]

DOI https://doi.org/10.1200/OP-24-00626

ABSTRACT

Indications for and implications of germline genetic testing (GGT) in patients with prostate cancer have expanded over the past decade, particularly related to precision therapies and management. GGT has become the standard of care for many cancers such as breast, ovarian, colorectal, pancreatic, and metastatic prostate cancer, and it is imperative that patients be offered timely and equitable access to testing as it can inform patient-physician shared decision making for management of the current cancer as well as anticipatory guidance for disease progression. Additionally, GGT guides screening for and prevention of secondary malignancies for the patient and cascade testing for at-risk family members. Here, we present data supporting the notion that clinicians should offer all patients with prostate cancer the opportunity to undergo comprehensive GGT for pathogenic germline variants known to be associated with familial cancer and/or known to have implications for treatment and management.

Accepted November 13, 2024
Published December 19, 2024

JCO Oncol Pract 21:747-753

View Online Article

Universal germline genetic testing (GGT) allows all patients with cancer, regardless of stage, pathology, or family history, to undergo GGT.[1-3] The importance of universal GGT has been highlighted by several studies which have demonstrated that guideline-directed GGT may miss up to 55% of patients with actionable pathogenic germline variants (PGVs).[4-7] A transition from guideline-directed to universal GGT has been recommended for breast, ovarian, and pancreatic cancers[8-10]; however, universal testing has not yet been recommended for prostate cancer.

Democratization of GGT by universal testing is particularly relevant for patients with prostate cancer, for whom there are multiple and sometimes conflicting guidelines for GGT published by various professional societies and consensus committees.[11-13] The National Comprehensive Cancer Network (NCCN) Prostate Cancer guidelines[14] have recently removed pretest guidelines for GGT and clinicians are now directed to the Hereditary Breast, Ovarian, and Pancreatic[15] and Hereditary Colorectal (Lynch syndrome) guidelines.[16] This recommendation change could result in additional barriers to testing as prostate cancer clinicians will now have to navigate to a different set of guidelines of which they are most likely not routinely familiar.

The complexity of the current criteria impedes real-world adoption of prostate cancer GGT. Accordingly, prostate cancer has one of the lowest rates of GGT utilization, with one contemporaneous study finding that only 1% of affected individuals underwent GGT.[17] Even in patients with metastatic and/or castration-resistant disease, for whom GGT is recommended, uptake of only 4%-13% has been reported.[17,18] GGT utilization is even worse among non-White, rural, and economically disadvantaged populations.[17,19] A systematic review by Briggs et al[19] found that only 7.2% of men undergoing GGT for prostate cancer were Black, significantly lower than the 13.4% of the US Black/African American population, and particularly concerning given the disproportionately high incidence of aggressive prostate cancer among Black men.[20] Additional studies have found racial disparities in genetic counseling referral rates and diagnostic yields from GGT.[5,21] In addition, restrictive GGT guidelines that rely on an accurate family history ascertainment are oftentimes a barrier for patients in whom this information may be incomplete or unavailable.[22] Moreover, histopathological features, such as grade group or intraductal/cribriform histology, which inform GGT eligibility, are subject to interobserver inconsistency within pathologic interpretations.[23]

Because GGT can inform patient-physician shared decision making, including therapeutic management, it is imperative that patients are offered timely and equitable access to GGT. Moreover, GGT is crucial for cascade testing of at-risk family

members, identifying those who would benefit from risk-reducing interventions and enhanced screening to detect early-stage malignancies, including not only prostate but also breast, ovarian, pancreas, and colorectal cancers. Thus, we recommend that all patients with prostate cancer should be offered comprehensive GGT for assessment of PGVs in genes that are associated with hereditary cancer and have implications for evaluation and management.

The prevalence of PGVs varies across the spectrum of prostate cancer. In patients with metastatic or advanced disease, the prevalence is 12%-20% across various DNA damage repair (DDR) genes, most commonly *BRCA2*.[4,24] Notably, somatic (acquired) mutations are identified in a similar proportion of patients with advanced disease,[4,25,26] but somatic-only sequencing misses 8%-17% of patients with PGVs because of technical/assay limitations, variant filtering, and variant classification differences.[27-29] Studies that included patients with broader stages of disease found PGV frequencies of 10%-17%, again with *BRCA2* being the most frequently identified, followed by *ATM*, *CHEK2*, and *HOXB13*.[5,30,31] PGVs occur in localized disease with a 3%-11% prevalence.[24,31-33] Many of these studies, however, were based on retrospective cohorts from genetic testing laboratories, high-risk cancer clinics, or biobanks of patients with advanced disease, and thus PGV rates may have been subject to ascertainment bias. Data generated from these selected populations have not been sufficient to promote universal GGT for men with prostate cancer.

Results from a recent prostate cancer GGT study provide strong evidence to consider GGT for all patients with prostate cancer.[7] The PROstate Cancer registry in Large patient population AIMed to assess efficacy in germline testing (PROCLAIM) trial investigated the impact of universal GGT in a prospective, unselected US population of patients from primarily community urology practices, where the majority of prostate cancer care occurs. Of the 958 patients with evaluable outcomes, approximately 50% met 2019 NCCN prostate cancer GGT guidelines and approximately 50% did not meet guidelines. The majority (65%) of patients had localized, low-risk or intermediate-risk disease. Overall, the prevalence of PGVs in the cohort was 7.7%. As predicted, the prevalence of PGVs did not differ significantly between patients meeting testing criteria and those not meeting criteria (8.8% *v* 6.6%, respectively). Most importantly, 42% of patients with PGVs would have been missed by guideline-restricted testing. Extrapolating these findings to the estimated incidence of 288,300 new patients diagnosed with prostate cancer in 2023,[34] restriction of GGT to only patients meeting test criteria may miss approximately 9,000 men with hereditary forms of prostate and other cancers each year.

Furthermore, in the PROCLAIM trial, PGVs were significantly more frequent in White compared with non-White patients (9.0 *v* 2.9%, respectively). Strikingly, among non-White patients, the PGV prevalence was nominally higher among patients who did not meet GGT criteria (4.0%) compared with those who did meet the criteria (1.8%), suggesting that guidelines may be unintentionally creating barriers to genetics-informed care in underrepresented and underserved populations. These data are supported by additional studies demonstrating that individuals from underrepresented populations and minorities were less likely to obtain PGV results and more likely to receive uncertain GGT results, compared with White individuals.[17,35-38] Allowing for broader GGT testing criteria should mitigate these disparities by increasing the number of (diverse) individuals tested, resulting in better representation of genetic variation.

Certain PGVs in patients with prostate cancer confer significant prognostic and predictive information. For example, PGVs in *BRCA2*, and possibly *BRCA1*, *ATM*, *NBN*, and *HOXB13*, are associated with more aggressive tumors, higher likelihood of progression to metastasis, and less favorable outcomes,[39-45] as well as higher risk of grade reclassification during active surveillance.[46] In particular, patients with *BRCA1*/*BRCA2* PGVs have a higher risk of metastasis and death from prostate cancer after local therapy (prostatectomy or external-beam radiation) compared with controls.[47,48] Accordingly, identification of a PGV in a high-risk gene is relevant for the management of localized, low-risk or intermediate-risk prostate cancer, as it can guide clinical strategies, including active surveillance protocols or an earlier definitive treatment approach.[14,47-51] Furthermore, studies have shown that germline DDR carriers with intermediate-risk or high-risk localized disease should not be excluded from intense neoadjuvant androgen deprivation therapy regimens on the basis of similar rates of exceptional pathologic response and biochemical recurrence after radical prostatectomy compared with noncarriers.[43]

Despite its underutilization, the utility of GGT is well established for advanced, metastatic, and resistant disease. Namely, PGV status is critical for determining eligibility for targeted therapies such as poly (ADP-ribose) polymerase inhibitors, which are now US Food and Drug Administration approved for both first and second-line therapy for metastatic castrate-resistant prostate cancer (Table 1)[73-77] and are being studied in the hormone-sensitive, localized high-risk, and maintenance therapy settings.[78-83] Furthermore, identification of a PGV in a mismatch repair (MMR) gene (*EPCAM*, *MLH1*, *MSH2*, *MHS6*, *PMS2*) is often an indication that the tumor may be MMR deficient and thus confers eligibility for treatment with the immune checkpoint inhibitor pembrolizumab.[84,85] Research has shown that patients with prostate cancer with germline or somatic pathogenic variants in DDR genes treated with radium-223 had an overall survival nearly twice as long as patients without DDR variants.[86] Additionally, consideration of other treatments such as early initiation of androgen deprivation therapy or platinum-based chemotherapies may be appropriate for individuals with PGVs in these genes.[87-89] Conversely, a recent study has identified worse outcomes for men with metastatic hormone-sensitive prostate cancer and *BRCA2*

TABLE 1. Gene-Specific Cancer Risks and Precision Management for Patients With Prostate Cancer With Germline Variants in NCCN-Recommended Prostate Cancer Genes

Gene With PGV	Prostate Cancer Risk Level (relative risk)	Non–Prostate Cancer Risks	NCCN Management Guidelines	Approved Targeted Therapy	Example Clinical Trials for Patients With Prostate Cancer[a]
ATM	Moderate (2-4×)[42,52,53]	Breast, pancreatic	Hereditary Breast, Ovarian and Pancreatic v.3.2024[54] Prostate Cancer Early Detection v.2.2024[55]	PARPi (olaparib, talazoparib)	NCT05011383 NCT04253262 NCT03810105 NCT02985021 NCT03413995 NCT04253262 NCT04812366 NCT04030559 NCT03047135
BRCA1 *BRCA2*	*BRCA1*: Moderate (1-3×)[56-58] *BRCA2*: High (2-8.5×)[48,58-60]	Breast, leukemia, melanoma, ovarian, pancreatic	Hereditary Breast, Ovarian and Pancreatic v.3.2024[54] Prostate Cancer Early Detection v.2.2024[55]	PARPi (niraparib, olaparib, rucaparib, talazoparib)	NCT05498272 NCT03810105 NCT02985021 NCT03413995 NCT04693468 NCT04253262 NCT04812366 NCT05806515 NCT04030559 NCT03047135 NCT02705846
CHEK2	Moderate (2-3×)[61-63]	Colorectal, renal, thyroid	Hereditary Breast, Ovarian and Pancreatic v.3.2024[54] Prostate Cancer Early Detection v.2.2024[55]	PARPi (olaparib, talazoparib)	NCT03810105 NCT03413995 NCT04030559 NCT03047135
HOXB13	High (3-8×)[64-66]	NA	Prostate Cancer Early Detection v.2.2024[55]	NA	NCT02705846
Mismatch repair genes (eg, *EPCAM, MLH1, MSH2, MSH6, PMS2*)	Moderate (2-3.5×;[67-69] *MSH2*: upto 6×[70])	Colorectal, endometrial, ovarian, gastric, small bowel, pancreatic urothelial	Hereditary Colorectal v.2.2023[16] Prostate Cancer Early Detection v.2.2024[55]	PD-1/PDL-1 inhibitor (pembrolizumab)	NCT03248570 NCT04126070 NCT02705846
PALB2	Moderate (1-3.5×)[24,45,71]	Breast, ovarian, pancreatic	Hereditary Breast, Ovarian and Pancreatic v.3.2024[54] Prostate Cancer Early Detection v.2.2024[55]	PARPi (olaparib, talazoparib)	NCT03810105 NCT03413995 NCT04693468 NCT04253262 NCT04030559 NCT03047135
TP53	High (1.5-9×)[45,72]	Breast, brain, colorectal, leukemia, lung, sarcoma	Hereditary Breast, Ovarian and Pancreatic v.3.2024[54] Prostate Cancer Early Detection v.2.2024[55]	NA	NCT06212583 NCT03903835

Abbreviations: NA, not applicable; NCCN, National Comprehensive Cancer Network; PARPi, poly (ADP-ribose) polymerase inhibitor; PGV, pathogenic germline variant.

[a]Clinical trials listed indicate a selection of ongoing trials for which patients with prostate cancer may be eligible and in which a germline pathogenic/likely pathogenic variant in the specified gene is among the inclusion criteria for enrollment. Trials have additional eligibility criteria not reported here; this table only reflects gene-based inclusion criteria.

PGVs undergoing androgen deprivation therapy alone.[90] Thus, establishing PGV status early in the disease course provides critical knowledge and anticipatory guidance for patients whose disease progresses, including those cured by localized treatment and those with hormone-sensitive disease.

Clinical trials are an added benefit of undergoing GGT, as eligibility criteria is often dependent on DDR gene status (Table 1).[2,91] Many of these trials are for localized prostate cancer in the active surveillance[92] or definitive treatment setting (eg, ClinicalTrials.gov identifiers: NCT05498272,[93] NCT04812366, NCT05806515, NCT04030559), where GGT guidelines are often dependent on complex family history criteria that could impede enrollment. Also, there are numerous trials in the advanced disease setting where GGT is recommended but often underutilized because it is not seen as necessary until the metastatic, castration-resistant setting when approved therapeutics can be considered. Therefore, it is important to broaden GGT guidelines to ensure access to both approved clinical care and clinical trials, to optimize care for all patients with prostate cancer.

Patients with PGVs in certain cancer predisposition genes are also at risk of other cancers, such as male breast cancer, colorectal cancer, pancreatic cancer, and melanoma (Table 1).[15,16] Individuals at risk of these cancers are encouraged to undergo increased surveillance (eg, mammograms/breast magnetic resonance imaging, colonoscopies, pancreatic cancer screening by using magnetic resonance cholangiopancreatography and endoscopic ultrasound) to detect cancers at an earlier, and potentially, curable stage.[15] One study found that among patients with cancer, 11% had PGVs identified only after presenting with a second primary cancer that possibly could have been detected earlier or prevented given current gene-specific surveillance and risk-reduction recommendations, hence representing a missed opportunity for individual patient disease detection or prevention and informing family members.[27] Accordingly, the cost savings associated with detecting cancer at earlier stages of diagnosis are significant, with treatment costs markedly less for early compared with late-stage diagnosis.[94]

In addition to improving patient management, universal GGT may benefit family members, enabling cascade family variant testing. Identifying unaffected family members with PGVs in both high-risk and moderate-risk genes is critically important for both cancer prevention and earlier diagnosis and their resulting reduction in health care costs, as well as lives saved through reduced cancer mortality.[95] Encouragingly, studies have shown that patients with prostate cancer value GGT for personal and familial implications, and they typically share their results with at least immediate family members.[96,97]

Recent research has measured the real-world clinical utility of universal GGT for patients with prostate cancer. Clinician-reported recommendations and outcomes for 982 patients from the PROCLAIM trial showed that GGT results influenced care for patients with prostate cancer, including those who did not meet NCCN testing criteria, and those with low-risk localized disease. Patients with positive results were significantly more likely than those with negative or uncertain results to receive recommendations for treatment changes ($P < .001$), follow-up changes ($P < .001$), and cascade testing ($P < .001$).[98] Additionally, negative results aided in shared decision making by reassuring clinicians and patients and contributing to de-escalation of interventional treatments.

A recommendation of GGT for all newly diagnosed patients with prostate cancer would represent a significant increase in the number of individuals eligible for testing, requiring additional implementation and educational resources. However, this is not an insurmountable challenge. In fact, the persisting shortage of genetic professionals has been an impetus for research devoted to harnessing technology and developing novel genetics service delivery models, many of which have been used in patients with prostate cancer.[99] Similar calls to action in breast cancer implore us to "no longer wait for a future with enough genetic counselors to test broadly."[100] Successful approaches to providing education and access to genetics care and counseling for patients with prostate cancer include pretest educational videos, telehealth, genetic testing stations staffed by genetic counselor extenders, and mainstream or hybrid approaches, where physicians order GGT after patients have received pretest education, followed by post-test, often remote, genetic counseling for patients with positive or uncertain results.[21,101-107] Because patients with prostate cancer prefer that discussion of, or referral to, genetics comes from one of their trusted providers,[96] mainstream or hybrid models have been particularly successful, resource efficient, and satisfactory for both clinicians and patients.[102,106,107] Accordingly, GGT uptake was high in these studies (75%-98%) as patients were particularly satisfied to have testing initiated at their existing oncology appointment rather than a separate genetics appointment.[102,106,107] Additionally, a variety of resources exist from professional societies for providers interested in incorporating GGT into their practices (Szymaniak et al[110] 2020; Mark et al[111] 2021), including Web-based modules and podcasts (Giri et al[112] 2021; Loeb et al[113] 2021). For practices without access to downstream genetics services, it may be feasible to add remote cancer genetic consultations to multidisciplinary tumor boards.[108] Ultimately, it will take collaboration among providers, patients, and genetic testing laboratories to streamline GGT into routine prostate cancer care.[99]

Additionally, the cost of GGT has substantially decreased over the past decade and is performed a single time with lifetime informative benefits for patients and relatives.[2,109] The one-time patient assessment using GGT is well recognized and distinct from the multiple-time-point utilization of other biomarkers (eg, imaging, urine, blood) throughout the patient's prostate cancer journey, including imaging, urine, and blood, about which there is ongoing debate regarding clinically indicated frequency and utility.

In conclusion, GGT is an important tool that enables personalized management of patients with prostate cancer, including access to approved prostate cancer therapeutics, opportunities for clinical trials, and testing of family members at risk of prostate cancer and other cancers. We believe that the body of evidence presented makes a strong case for comprehensive GGT for all patients diagnosed with prostate cancer independent of stage or family history. Prostate cancer is one of the most common hereditary cancers, along with breast, ovarian, pancreatic, and colorectal cancers, and guidelines for the aforementioned cancers have all transitioned to either recommendation or consideration of universal testing[8,15,16]; prostate cancer should not be the exception.

AFFILIATIONS

[1]Carolina Urologic Research Center, Myrtle Beach, SC
[2]Labcorp Genetics Inc (formerly Invitae Corp), San Francisco, CA
[3]University of Minnesota, Masonic Cancer Center, Minneapolis, MN
[4]Case Western Reserve University, Cleveland, OH
[5]The Knight Cancer Institute, Oregon Health & Science University, Portland, OR
[6]Exact Sciences Corporation, Madison, WI
[7]Dana Faber Cancer Institute, Boston, MA
[8]City of Hope Cancer Center, Goodyear, AZ
[9]Stephenson Cancer Center, OU Health, The University of Oklahoma, Oklahoma City, OK
[10]University California, San Diego, La Jolla, CA
[11]Duke Cancer Institute, Duke University, Durham, NC
[12]Karmanos Cancer Institute, Detroit, MI
[13]NorthShore University HealthSystem/Endeavor Health, Evanston, IL
[14]Northwestern Feinberg School of Medicine, Chicago, IL
[15]Memorial Sloan Kettering Cancer Center, New York, NY
[16]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD
[17]Mayo Clinic, Rochester, MN
[18]UCLA David Geffen School of Medicine, Los Angeles, CA
[19]Keystone Urology Specialists, Lancaster, PA
[20]Massachusetts General Hospital, Boston, MA
[21]Perlmutter Cancer Center, NYU Langone Health, New York, NY

CORRESPONDING AUTHOR

Neal Shore, MD; Twitter: @nealshore; e-mail: nshore@auclinics.com.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP-24-00626.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Sarah M. Nielsen, Edward D. Esplin
Collection and assembly of data: Neal Shore, Sarah M. Nielsen
Data analysis and interpretation: Neal Shore, Sarah M. Nielsen
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank Rachel E. Ellsworth (Labcorp Genetics, Inc) for her copyediting. FTE and writing support provided by Labcorp Genetics (formerly Invitae Corporation).

REFERENCES

1. Esplin ED, Nielsen SM, Bristow SL, et al: Universal germline genetic testing for hereditary cancer syndromes in patients with solid tumor cancer. JCO Precis Oncol 10.1200/PO.21.00516
2. Subbiah V, Kurzrock R: Universal germline and tumor genomic testing needed to win the war against cancer: Genomics is the diagnosis. J Clin Oncol 41:3100-3103, 2023
3. Armstrong AJ, Taylor A, Haffner MC, et al: Germline and somatic testing for homologous repair deficiency in patients with prostate cancer (part 1 of 2). Prostate Cancer Prostatic Dis 10.1038/s41391-024-00901-4 [epub ahead of print on October 1, 2024]
4. Mandelker D, Zhang L, Kemel Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 318:825-835, 2017
5. Nicolosi P, Ledet E, Yang S, et al: Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 5:523-528, 2019
6. Samadder NJ, Riegert-Johnson D, Boardman L, et al: Comparison of universal genetic testing vs guideline-directed targeted testing for patients with hereditary cancer syndrome. JAMA Oncol 7: 230-237, 2021
7. Shore N, Gazi M, Pieczonka C, et al: Efficacy of National Comprehensive Cancer Network guidelines in identifying pathogenic germline variants among unselected patients with prostate cancer: The PROCLAIM trial. Eur Urol Oncol 6:477-483, 2023
8. Manahan ER, Kuerer HM, Sebastian M, et al: Consensus guidelines on genetic` testing for hereditary breast cancer from the American Society of Breast Surgeons. Ann Surg Oncol 26:3025-3031, 2019
9. Daly MB, Pal T, Maxwell KN, et al: NCCN Guidelines® Insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2024. J Natl Compr Canc Netw 21:1000-1010, 2023
10. National Comprehensive Cancer Network: NCCN Guidelines Version 1.2020 High-Risk Colorectal Cancer Syndromes. 2019
11. Schaeffer EM, Srinivas S, Adra N, et al: NCCN Guidelines® Insights: Prostate cancer, version 1.2023. J Natl Compr Canc Netw 20:1288-1298, 2022
12. Giri VN, Knudsen KE, Kelly WK, et al: Implementation of germline testing for prostate cancer: Philadelphia prostate cancer consensus conference 2019. J Clin Oncol 38:2798-2811, 2020
13. Eastham JA, Auffenberg GB, Barocas DA, et al: Clinically localized prostate cancer: AUA/ASTRO guideline, Part I: Introduction, risk assessment, staging, and risk-based management. J Urol 208: 10-18, 2022
14. Schaeffer EM, Srinivas S, Adra N, et al: National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Prostate Cancer (Version 3.2024), 2024. https://www.nccn.org
15. Daly MB, Pal T, Arun B, et al: National Comprehensive Cancer Network. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2025), 2024. https://www.nccn.org
16. Gupta S, Weiss JM, Axell L, et al: National Comprehensive Cancer Network. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Colorectal (Version 2.2023). NCCN, 2023. https://www.nccn.org
17. Kurian AW, Abrahamse P, Furgal A, et al: Germline genetic testing after cancer diagnosis. JAMA 330:43-51, 2023
18. Shore N, Ionescu-Ittu R, Yang L, et al: Real-world genetic testing patterns in metastatic castration-resistant prostate cancer. Future Oncol 17:2907-2921, 2021
19. Briggs LG, Steele GL, Qian ZJ, et al: Racial differences in germline genetic testing for prostate cancer: A systematic review. JCO Oncol Pract 19:e784-e793, 2023
20. Lillard JW Jr, Moses KA, Mahal BA, et al: Racial disparities in Black men with prostate cancer: A literature review. Cancer 128:3787-3795, 2022
21. Kwon DH, Gordon KM, Tong B, et al: Implementation of a telehealth genetic testing station to deliver germline testing for men with prostate cancer. JCO Oncol Pract 19:e773-e783, 2023
22. Lynn B, Hatry A, Burnett C, et al: Identifying primary care physicians continuing education needs by examining clinical practices, attitudes, and barriers to screening across multiple cancers. J Cancer Educ 33:1255-1262, 2018

23. Flach RN, Willemse PPM, Suelmann BBM, et al: Significant inter- and intralaboratory variation in Gleason grading of prostate cancer: A nationwide study of 35,258 patients in the Netherlands. Cancers (Basel) 13:5378, 2021
24. Pritchard CC, Mateo J, Walsh MF, et al: Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 375:443-453, 2016
25. Armenia J, Wankowicz SAM, Liu D, et al: The long tail of oncogenic drivers in prostate cancer. Nat Genet 50:645-651, 2018
26. Truong H, Breen K, Nandakumar S, et al: Gene-based confirmatory germline testing following tumor-only sequencing of prostate cancer. Eur Urol 83:29-38, 2023
27. Lincoln SE, Nussbaum RL, Kurian AW, et al: Yield and utility of germline testing following tumor sequencing in patients with cancer. JAMA Netw Open 3:e2019452, 2020
28. Terraf P, Pareja F, Brown DN, et al: Comprehensive assessment of germline pathogenic variant detection in tumor-only sequencing. Ann Oncol 33:426-433, 2022
29. Berchuck JE, Boiarsky D, Silver R, et al: Addition of germline testing to tumor-only sequencing improves detection of pathogenic germline variants in men with advanced prostate cancer. JCO Precis Oncol 10.1200/PO.22.00329
30. Giri VN, Hegarty SE, Hyatt C, et al: Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate 79:333-339, 2019
31. Pritzlaff M, Tian Y, Reineke P, et al: Diagnosing hereditary cancer predisposition in men with prostate cancer. Genet Med 22:1517-1523, 2020
32. Greenberg SE, Hunt TC, Ambrose JP, et al: Clinical germline testing results of men with prostate cancer: Patient-level factors and implications of NCCN guideline expansion. JCO Precis Oncol 10.1200/PO.20.00432
33. Lee DJ, Hausler R, Le AN, et al: Association of inherited mutations in DNA repair genes with localized prostate cancer. Eur Urol 81:559-567, 2022
34. Siegel, RL, Miller, KD, Wagle, NS, et al Cancer statistics, 2023. CA Cancer J Clin 73:17-48, 2023
35. Ndugga-Kabuye MK, Issaka RB: Inequities in multi-gene hereditary cancer testing: Lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European. Fam Cancer 18:465-469, 2019
36. Yadav S, LaDuca H, Polley EC, et al: Racial and ethnic differences in multigene hereditary cancer panel test results for women with breast cancer. J Natl Cancer Inst 113:1429-1433, 2021
37. Bree KK, Hensley PJ, Pettaway CA: Germline mutations in African American men with prostate cancer: Incidence, implications and diagnostic disparities. Urology 163:148-155, 2022
38. Soewito S, Wyatt R, Berenson E, et al: Disparities in cancer genetic testing and variants of uncertain significance in the Hispanic population of South Texas. JCO Oncol Pract 18:e805-e813, 2022
39. Castro E, Goh C, Olmos D, et al: Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 31: 1748-1757, 2013
40. Na R, Zheng SL, Han M, et al: Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 71:740-747, 2017
41. Castro E, Romero-Laorden N, Del Pozo A, et al: PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 37:490-503, 2019
42. Nguyen-Dumont T, Dowty JG, MacInnis RJ, et al: Rare germline pathogenic variants identified by multigene panel testing and the risk of aggressive prostate cancer. Cancers 13:1495, 2021
43. Berchuck JE, Zhang Z, Silver R, et al: Impact of pathogenic germline DNA damage repair alterations on response to intense neoadjuvant androgen deprivation therapy in high-risk localized prostate cancer. Eur Urol 80:295-303, 2021
44. Kanayama M, Chen Y, Rabizadeh D, et al: Clinical and functional analyses of an African-ancestry gain-of-function HOXB13 variant implicated in aggressive prostate cancer. Eur Urol Oncol 7: 751-759, 2024
45. Darst BF, Saunders E, Dadaev T, et al: Germline sequencing analysis to inform clinical gene panel testing for aggressive prostate cancer. JAMA Oncol 9:1514-1524, 2023
46. Carter HB, Helfand B, Mamawala M, et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 75: 743-749, 2019
47. Castro E, Goh C, Leongamornlert D, et al: Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 68:186-193, 2015
48. Oh M, Alkhushaym N, Fallatah S, et al: The association of BRCA1 and BRCA2 mutations with prostate cancer risk, frequency, and mortality: A meta-analysis. Prostate 79:880-895, 2019
49. Helfand BT, Xu J: Germline testing for prostate cancer prognosis: Implications for active surveillance. Can J Urol 26:48-49, 2019 (5 suppl 2)
50. Rajwa P, Quhal F, Pradere B, et al: Prostate cancer risk, screening and management in patients with germline BRCA1/2 mutations. Nat Rev Urol 20:205-216, 2023
51. Amini AE, Salari K: Incorporating genetic risk into prostate cancer care: Implications for early detection and precision oncology. JCO Precis Oncol 10.1200/PO.23.00560
52. Hall MJ, Bernhisel R, Hughes E, et al: Germline pathogenic variants in the Ataxia Telangiectasia Mutated (ATM) gene are associated with high and moderate risks for multiple cancers. Cancer Prev Res 14:433-440, 2021
53. Karlsson Q, Brook MN, Dadaev T, et al: Rare germline variants in ATM predispose to prostate cancer: A PRACTICAL consortium study. Eur Urol Oncol 4:570-579, 2021
54. Daly MB, Pal T, AlHilli Z, et al: NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 3.2024). 2024. https://www.nccn.org
55. Moses KA, Sprenkle PC, Bahler C, et al: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer Early Detection Version 2.2024. https://www.nccn.org
56. Thompson D, Easton DF; Breast Cancer Linkage Consortium: Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358-1365, 2002
57. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al: Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 106:1697-1701, 2012
58. Nyberg T, Frost D, Barrowdale D, et al: Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: A prospective cohort study. Eur Urol 77:24-35, 2020
59. Kote-Jarai Z, Leongamornlert D, Saunders E, et al: BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: Implications for genetic testing in prostate cancer patients. Br J Cancer 105:1230-1234, 2011
60. Silvestri V, Leslie G, Barnes DR, et al: Characterization of the cancer spectrum in men with germline BRCA1 and BRCA2 pathogenic variants: Results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). JAMA Oncol 6:1218-1230, 2020
61. Hale V, Weischer M, Park JY: CHEK2*1100delC mutation and risk of prostate cancer. Prostate Cancer 2014:294575, 2014
62. Wang Y, Dai B, Ye D: CHEK2 mutation and risk of prostate cancer: A systematic review and meta-analysis. Int J Clin Exp Med 8:15708-15715, 2015
63. Wu Y, Yu H, Zheng SL, et al: A comprehensive evaluation of CHEK2 germline mutations in men with prostate cancer. Prostate 78:607-615, 2018
64. Ewing CM, Ray AM, Lange EM, et al: Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 366:141-149, 2012
65. Xu J, Lange EM, Lu L, et al: HOXB13 is a susceptibility gene for prostate cancer: Results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 132:5-14, 2013
66. Nyberg T, Govindasami K, Leslie G, et al: Homeobox B13 G84E mutation and prostate cancer risk. Eur Urol 75:834-845, 2019
67. Raymond VM, Mukherjee B, Wang F, et al: Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 31:1713-1718, 2013
68. Ryan S, Jenkins MA, Win AK: Risk of prostate cancer in Lynch syndrome: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 23:437-449, 2014
69. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al: Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the Prospective Lynch Syndrome Database. Genet Med 22:15-25, 2020
70. Rosty C, Walsh MD, Lindor NM, et al: High prevalence of mismatch repair deficiency in prostate cancers diagnosed in mismatch repair gene mutation carriers from the colon cancer family registry. Fam Cancer 13:573-582, 2014
71. Wokołorczyk D, Kluźniak W, Stempa K, et al: PALB2 mutations and prostate cancer risk and survival. Br J Cancer 125:569-575, 2021
72. Maxwell KN, Cheng HH, Powers J, et al: Inherited TP53 variants and risk of prostate cancer. Eur Urol 81:243-250, 2022
73. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
74. Abida W, Patnaik A, Campbell D, et al: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 38:3763-3772, 2020
75. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al: Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid 1:EVIDoa2200043, 2022
76. Agarwal N, Azad AA, Carles J, et al: Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): A randomised, placebo-controlled, phase 3 trial. Lancet 402:291-303, 2023
77. Chi KN, Rathkopf D, Smith MR, et al: Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol 41:3339-3351, 2023
78. Antonarakis ES, Wang H, Teply BA, et al: Interim results from a phase 2 study of olaparib (without ADT) in men with biochemically-recurrent prostate cancer after prostatectomy, with integrated biomarker analysis. J Clin Oncol 37, 2019 (suppl 15; abstr 5045)
79. Rathkopf DE, Chi KN, Olmos D, et al: AMPLITUDE: A study of niraparib in combination with abiraterone acetate plus prednisone (AAP) versus AAP for the treatment of patients with deleterious germline or somatic homologous recombination repair (HRR) gene-altered metastatic castration-sensitive prostate cancer (mCSPC). J Clin Oncol 39, 2021 (suppl 6; abstr TPS176)
80. Agarwal N, Saad F, Azad A, et al: TALAPRO-3: A phase 3, double-blind, randomized study of enzalutamide (ENZA) plus talazoparib (TALA) vs placebo plus ENZA in patients with DDR gene-mutated, metastatic castration-sensitive prostate cancer (mCSPC). J Clin Oncol 41, 2023 (suppl 6; abstr TPS279)
81. Markowski MC, Sternberg CN, Wang H, et al: TRIUMPH: Phase II trial of rucaparib monotherapy in patients with metastatic hormone-sensitive prostate cancer harboring germline DNA repair gene mutations. J Clin Oncol 41, 2023 (suppl 6; abstr 190)

82. Dall'era M, McPherson J, Evans CP, et al: Neo-adjuvant PARP inhibition prior to prostatectomy: A phase II biomarker-driven trial for men with high-risk, localized prostate cancer and alterations in DNA repair genes. J Clin Oncol 41, 2023 (suppl 6; abstr TPS401)
83. Juan Fita MJ, Anido Herranz U, Mendez Vidal MJ, et al: Phase II trial evaluating olaparib maintenance in patients with metastatic castration resistant prostate cancer (mCRPC) after docetaxel treatment, reaching partial or stable response: SOGUG-IMANOL study. J Clin Oncol 41, 2023 (suppl 6; abstr 168)
84. Hansen AR, Massard C, Ott PA, et al: Pembrolizumab for advanced prostate adenocarcinoma: Findings of the KEYNOTE-028 study. Ann Oncol 29:1807-1813, 2018
85. Patel L, Pritchard CC: Molecular testing of DNA damage response pathways in prostate cancer patients. Curr Opin Oncol 35:224-230, 2023
86. van der Doelen MJ, Isaacsson Velho P, Slootbeek PHJ, et al: Impact of DNA damage repair defects on response to radium-223 and overall survival in metastatic castration-resistant prostate cancer. Eur J Cancer 136:16-24, 2020
87. Pomerantz MM, Spisák S, Jia L, et al: The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 123:3532-3539, 2017
88. Mota JM, Barnett E, Nauseef JT, et al: Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. JCO Precis Oncol 10.1200/PO.19.00346
89. Finch A, Clark R, Vesprini D, et al: An appraisal of genetic testing for prostate cancer susceptibility. npj Precis Oncol 6:43, 2022
90. Hamid A, Chinsky TM, Vergara M, et al: Landscape and impact of germline pathogenic variants (PVs) in metastatic hormone sensitive prostate cancer (mHSPC): Ancillary study of E3805 CHAARTED. J Clin Oncol 41, 2023 (suppl 16; abstr 5082)
91. Kammula AV, Schäffer AA, Rajagopal PS: Characterization of oncology clinical trials using germline genetic data. JAMA Netw Open 5:e2242370, 2022
92. Carlo MI: Impact of Germline Genetic Testing for Men with Prostate Cancer on Active Surveillance. Department of Defense: Defense Technical Information Center, 2022. https://apps.dtic.mil/sti/citations/trecms/AD1172219
93. McKay RR, Liu L, Pu M, et al: A phase 2 study of neoadjuvant PARP inhibition followed by radical prostatectomy (RP) in patients with unfavorable intermediate-risk or high-risk prostate cancer with BRCA1/2 gene alterations (NePtune). J Clin Oncol 42, 2024 (suppl 16; abstr TPS353)
94. Kakushadze Z, Raghubanshi R, Yu W: Estimating cost savings from early cancer diagnosis. Data 2:30, 2017
95. Whitaker KD, Obeid E, Daly MB, et al: Cascade genetic testing for hereditary cancer risk: An underutilized tool for cancer prevention. JCO Precis Oncol 10.1200/PO.21.00163
96. Greenberg S, Slager S, Neil BO, et al: What men want: Qualitative analysis of what men with prostate cancer (PCa) want to learn regarding genetic referral, counseling, and testing. Prostate 80:441-450, 2020
97. Leader AE, Mercado J, Klein A, et al: Insight into how patients with prostate cancer interpret and communicate genetic test results: Implications for families. J Community Genet 13:547-556, 2022
98. Shore N, Pieczonka C, Heron S, et al: Clinician-reported management recommendations in response to universal germline genetic testing in patients with prostate cancer. J Urol 212:832-843, 2024
99. Shore N, Wise D, Young SN: Understanding the Underutilization of Germline Genetic Testing in Prostate Cancer. ASCO Daily News. 2023. https://dailynews.ascopubs.org/do/understanding-underutilization-germline-genetic-testing-prostate-cancer
100. Rajagopal PS, Catenacci DVT, Olopade OI: The time for mainstreaming germline testing for patients with breast cancer is now. J Clin Oncol 37:2177-2178, 2019
101. Sokolova A, Miyamoto AN, Pouv DL, et al: Implementation of systematic germline genetic testing (GT) for metastatic prostate cancer (mPC) patients at the Puget Sound VA prostate oncology clinic. J Clin Oncol 38, 2020 (suppl 15; abstr 1578)
102. Scheinberg T, Goodwin A, Ip E, et al: Evaluation of a mainstream model of genetic testing for men with prostate cancer. JCO Oncol Pract 17:e204-e216, 2021
103. Russo J, McDougall C, Bowler N, et al: Pretest genetic education video versus genetic counseling for men considering prostate cancer germline testing: A patient-choice study to address urgent practice needs. JCO Precis Oncol 10.1200/PO.21.00238
104. Greenberg S, Orlando E, Devlin M, et al: Comparing pretest video genetic education for prostate cancer patients: Do patients need assistance? J Clin Oncol 40, 2022 (suppl 16; abstr 5061)
105. Loeb S, Cheng HH, Leader A, et al: Technology-enhanced AcceleRation of Germline Evaluation for Therapy (TARGET): A randomized controlled trial of a pretest patient-driven webtool vs. genetic counseling for prostate cancer germline testing. Contemp Clin Trials 119:106821, 2022
106. Abusamra SM, Solorzano MA, Luke M, et al: Satisfaction with clinician-led germline genetic counseling in patients with prostate cancer. J Urol 208:1007-1017, 2022
107. Breen KE, Symecko H, Spielman K, et al: Clinical impact of a rapid genetic testing model for advanced prostate cancer patients. J Urol 209:918-927, 2023
108. Santos LG, Buzdnitskaya T, Rolf BA, et al: Assessment of a peer physician coaching partnership between a designated cancer center genetics service and a community cancer network hospital. JAMA Netw Open 6:e231723, 2023
109. Kris A, Wetterstrand MS: DNA Sequencing Costs: Data, 2019. https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data
110. Szymaniak, BM, Facchini LA, Giri VN, et al: Practical considerations and challenges for germline genetic testing in patients with prostate cancer: Recommendations from the germline genetics working group of the PCCTC. JCO Oncol Pract 16:811-819, 2020
111. Mark JR, McDougall C, Giri VN: Genetic testing guidelines and education of health care providers involved in prostate cancer care. Urol Clin North Am 48:311-322, 2021
112. Giri VN, Walker A, Gross L, et al: Helix: A digital tool to address provider needs for prostate cancer genetic testing in clinical practice. Clin Genitourin Cancer 20:e104-e113, 2022
113. Loeb S, Sanchez Nolasco T, Siu K, et al: Usefulness of podcasts to provide public education on prostate cancer genetics. Prostate Cancer Prostatic Dis 26:772-777, 2023

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Implementation of Universal Germline Genetic Testing Into Standard of Care for Patients With Prostate Cancer: The Time Is Now

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).
No potential conflicts of interest were reported.