Implementing and Optimizing Universal Germline Genetic Testing for Patients With Prostate Cancer in Clinical Practice

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OBJECTIVE To advocate for universal germline genetic testing (UGGT) in prostate cancer and provide practical recommendations for its implementation.

METHODS Although guidelines for germline genetic testing in prostate cancer have progressed, usage remains limited and inconsistent due to barriers including access, cost, and variable guideline adherence. These issues prevent some patients with germline pathogenic/likely pathogenic variants from benefiting from risk assessment, precision therapies (eg, PARP inhibitors, PD-1 inhibitors), and potential clinical trials. Despite these benefits, studies indicate that germline genetic testing use remains low, especially in prostate cancer care. The PROCLAIM trial (Shore et al, 2023) highlighted that nearly half of patients with pathogenic variants are missed under National Comprehensive Cancer Network guidelines, particularly impacting non-white patients and those with incomplete family history data. Additional racial and socioeconomic disparities further hinder access and variant interpretation accuracy. Given these challenges, UGGT for all prostate cancer patients has been proposed to improve care equity and decision-making. In March 2024, prostate cancer experts convened to discuss strategies for UGGT implementation.

RESULTS The outcome of that meeting includes recommendations for integrating UGGT into oncology and urology practices and have been outlined in this paper.

CONCLUSION To maximize the benefits while mitigating the potential risks of UGGT, it is essential to address implementation details, including careful gene panel selection, variants of uncertain significance reporting and management, appropriate genetics follow-up, and seamless integration of test reports into electronic medical records for accessibility by patients and providers. UROLOGY xx: xxx–xxx, xxxx. © 2025 Published by Elsevier Inc.

INTRODUCTION

In 2024, ≈299,010 men were diagnosed with prostate cancer (PCa) in the US, making it the most prevalent cancer at 29%[1]; furthermore, PCa caused ≈35,250 deaths, making it the second leading cause of cancer-related mortality at 11%. ≈5%-20% of all patients with PCa harbor a pathogenic/likely pathogenic germline variant (PGV), with varying rates depending on the stage of disease.[2–7] PGV in genes responsible for deoxyribonucleic acid (DNA) damage repair, such as *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, and *PALB2* are associated with PCa.[5] Furthermore, tumor mutations in *MLH1*, *MSH2*, *MSH6*, *and PMS2* may result in tumor microsatellite instability (MSI) and deficient MMR (dMMR), which may be associated with germline mutations and Lynch syndrome, leading to an increased risk for PCa.[8,9] PCa patients with certain PGVs, particularly those involved in homologous recombination repair (HRR), have more aggressive disease leading to early progression and a potential for worsening prognosis.[10,11]

Clinical trials have highlighted the critical role of genetic testing in guiding precision therapies for PCa. The PROFOUND trial demonstrated that the Poly (ADP-ribose) polymerase inhibitor (PARPi) olaparib

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significantly improved progression-free survival and overall survival in patients with metastatic castration-resistant PCa (mCRPC) who demonstrated HRR mutations (HRRm), leading to U.S. Food and Drug Administration (FDA) approval in 2020. The PROpel,[12] MAGNITUDE,[13] and TALAPRO-2[14] phase 3 trials evaluated combination therapies with olaparib, niraparib, and talazoparib, respectively, in patients with or without HRRm and achieved FDA approval in 2023. The KEYNOTE-158 study demonstrated the efficacy of pembrolizumab, a PD-1 inhibitor, in patients with advanced solid tumors, including those with microsatellite instability-High or deficient MMR cancers, commonly associated with Lynch syndrome.[15,16] These trials successfully led to several therapeutic approvals globally.

The value of genetic testing in tumors (tumor profiling) for identifying markers that guide systemic treatment is well recognized. In metastatic PCa, ≈25% of tumor samples show clinically actionable variants,[17] while ≈12% have PGV.[5] However, relying upon tumor testing may fail to detect PGV. Studies in various tumor types have found that 8%-35% of PGVs are missed by tumor-only testing.[18,19] Paired tumor and germline testing is crucial for guiding systemic therapy in advanced PCa. While tumor testing identifies mutations present in the cancerous tissue, germline genetic testing (GGT) examines inherited genetic variants. By integrating both, clinicians can distinguish somatic mutations (those arising in the tumor) from PGV (those that are inherited), thus providing a more accurate understanding of a patient's cancer profile. This combined approach strengthens the case for conducting germline testing on everyone, as it offers essential context for interpreting tumor results, leading to more informed treatment decisions and personalized care.

Limitations of Current Guidelines for GGT

Several guidelines, including those from the European Association of Urology, the National Comprehensive Cancer Network (NCCN), the Advanced PCa Consensus Conference, the Philadelphia PCa Consensus, and American Urological Association have addressed considerations for GGT in PCa.

Despite these attempts, a significant number of patients with PGVs are going undiagnosed, because of **(A)** limitations of the current guidelines in successfully discerning the patients at risk, **(B)** scarcity of the resources needed to implement GGT (ie, provider space, time, cost, processes/workflow challenges, lack of educational materials, and limited access to genetic counselors [GC]), which also affects veterans—a population at elevated risk for PCa, and **(C)** the complexity of the current guidelines being a barrier for physician assessment of patient eligibility. For members of the Black community, medical mistrust due to historical abuse has been documented as a reason for the underutilization of GGT.[20]

NCCN guidelines and biopsy Gleason scores cannot reliably predict PGV presence. In the PROCLAIM trial, a cohort of 958 unselected PCa patients underwent GGT across 15 primarily community urology practices. The study found that 9.5% of these patients carried PGVs, with a substantial number not meeting the existing NCCN guidelines for testing. The results suggest that current guidelines may miss a significant proportion of patients with PGVs, particularly affecting non-White populations, indicating a need for broader GGT criteria to better identify at-risk individuals and inform targeted treatment strategies.[7] A potential reason could be that current guidelines necessitate the use of family histories, which are often not known or well communicated, thus limiting the identification of patients eligible for GGT. Another study demonstrated that approximately 74% of patients with HRR defects were not being tested under current guidelines, leaving their PGVs undetected.[21]

While Gleason 6 or GG1 cancer is very low risk at biopsy, some cases are later upgraded at prostatectomy. The 2014 ISUP GG system reduced upgrading rates compared to the 2005 classification (895/9703: 19.5% vs 2332/9703: 24.0%; $P = 0.001$).[22] Prostate biopsies are subjected to serious sampling errors, and mpMRI can miss clinically significant cancer.[23]

A study by Mandelker et al comparing universal sequencing of cancer-related genes in tumor and normal DNA to guideline-based germline testing in advanced cancer patients showed that universal sequencing identified significantly more PGVs, including those missed by traditional testing methods.[3] Similarly, Nicolosi et al investigated the prevalence of germline variants in PCa and found that current genetic testing guidelines missed a substantial number of germline variants.[4] Both studies advocated for expanding genetic testing to improve detection and treatment strategies for cancer patients. Another study conducted by Aguiar et al indicated that utilization rates of genetic testing remained low in all patient groups, including mCRPC, where genetic testing could identify patients with HRRm who may benefit from the use of targeted therapeutics such as PARPi.[24]

It is worth noting that although the chances of finding PGVs are highest when the disease is metastatic, the utility of GGT can also serve in management decisions for even low and intermediate risk disease. Although no guidelines exist for managing germline mutations in localized PCa, emerging evidence suggests *BRCA2* carriers on active surveillance (AS) face higher rates of biopsy upgrading and more aggressive disease.[25] Genetic testing may help tailor monitoring and treatment strategies, such as intensified surveillance or prioritizing surgery with full pathology review and lymph node dissection. However, physicians should disclose the limitations of germline testing for AS due to limited data.

Considering factors **(A)** and **(C)** (as described above), broader testing based on individual disease characteristics under a universal germline genetic testing (UGGT) paradigm would identify more patients with PGV and simplify the patient selection process. UGGT would offer GGT to all PCa patients to inform treatment decisions. The UGGT model has been explored with promising

results. The INTERCEPT trial (2984 patients) showed that universal multigene testing increased detection of heritable variants, leading to treatment modifications in nearly 30% of cases.[6]

Routine implementation of UGGT would reveal a higher number of cases that are currently missed under the existing guidelines and facilitate more personalized and effective management of PCa across all risk groups.[7] UGGT could also help close the germline testing gap among racial/ethnic minorities and reduce inequities in PCa screening, management, and treatment.

Considerations or Risks of UGGT

UGGT enables early detection of advanced diseases, screening for additional health risks, and insights into familial implications but faces key challenges. Misinterpretation of variants of uncertain significance (VUS) is common; 13% of patients in a study by Dr. Giri's team,[26] mistakenly believed a VUS was a positive result. Inefficiencies in variant reclassification, especially in systems lacking automated processes or dedicated GC, can leave patients misinformed. Risks include using labs without automatic reclassification and insufficient pre-test education, increasing misinterpretation. Identifying PGVs in non-actionable conditions may cause psychological distress and raise concerns about related cancer risks (eg, pancreatic, breast, colon) for patients and families. A 2024 review[27] suggests cascade testing to address familial implications, but implementation challenges persist. To realize UGGT's potential, these risks must be managed effectively.

Practical Considerations for Implementing UGGT

In this paper, we review practical considerations for implementing UGGT to improve efficiency while preserving high quality testing, clinical utility, and patient satisfaction in order to address the aforementioned limitations, particularly **(B)**—the scarcity of resources (Fig. 1 and Table 1).

The UGGT approach is divided into pre- and post-test education and is ideally multidisciplinary (involving physicians (eg, oncologists, urologists), allied healthcare professionals (HCP) [nurses, physician assistants], and GC. The considerations herein focus on the role of GGT in actively guiding clinical care. They do not cover genetic testing for PCa risk, newer testing methodologies, or somatic testing in depth, albeit these are important areas of education and could be augmented by incorporating the UGGT model.

Pre-Test Education

- What is it?
  - Pre-test education supports informed consent for GGT. This involves explaining the testing process, potential outcomes, and implications for patients and families.
- Who provides it?
  - GC have traditionally provided pre-test education, but when case volume is high or access is limited, other HCP can facilitate this. "Mainstreaming" or "point-of-care" testing integrates pre-test education into physicians' practices, with nurses, physician assistants, or chatbots offering support. This approach improves accessibility, builds trust, and enhances personalized treatment strategies.
- How is it done?
  - A practical way to improve pre-test education is to use a standardized, tiered approach tailored to patient needs and test complexity, starting with clear, accessible materials (eg, brochures, videos) and a checklist covering the test purpose, outcomes, risks, and patient concerns.
  - Using decision aids (eg, risk-benefit charts or Yvonne Bombards Genomics ADvISER), emotional support, and chatbots enhances patient understanding, informed consent, and psychological readiness, improving clinical and patient outcomes.
  - Post-COVID-19, telemedicine became popular for its accessibility and convenience, overcoming geographic and scheduling barriers to provide feasible GC services, as shown in a large registry.
  - If patients have more questions, they can be referred to a local GC, if available, or a third-party company that provides pre-test genetic counseling.
- What topics should be covered?
  - Explain the reasons for testing.
    - The primary goal is to inform treatment decisions (eg, systemic therapy, AS, prostatectomy vs radiation +/- hormone therapy). Secondary goals include assessing risk for other hereditary cancers and cascade testing for family members.
    - Reassure patients by emphasizing the benefits of GGT, for example, personalized care and insights for family. Clear communication and support are key, with negative results offering reassurance and aiding shared decision-making, potentially reducing unnecessary interventions.
  - Disclose the limitations of testing
    - Technology's ability to identify PGV in the known genes
    - Ability to accurately interpret variants that were identified to determine if they are disease-causing
    - Evolving knowledge of the most relevant genes to test
  - Discuss the possible types of results

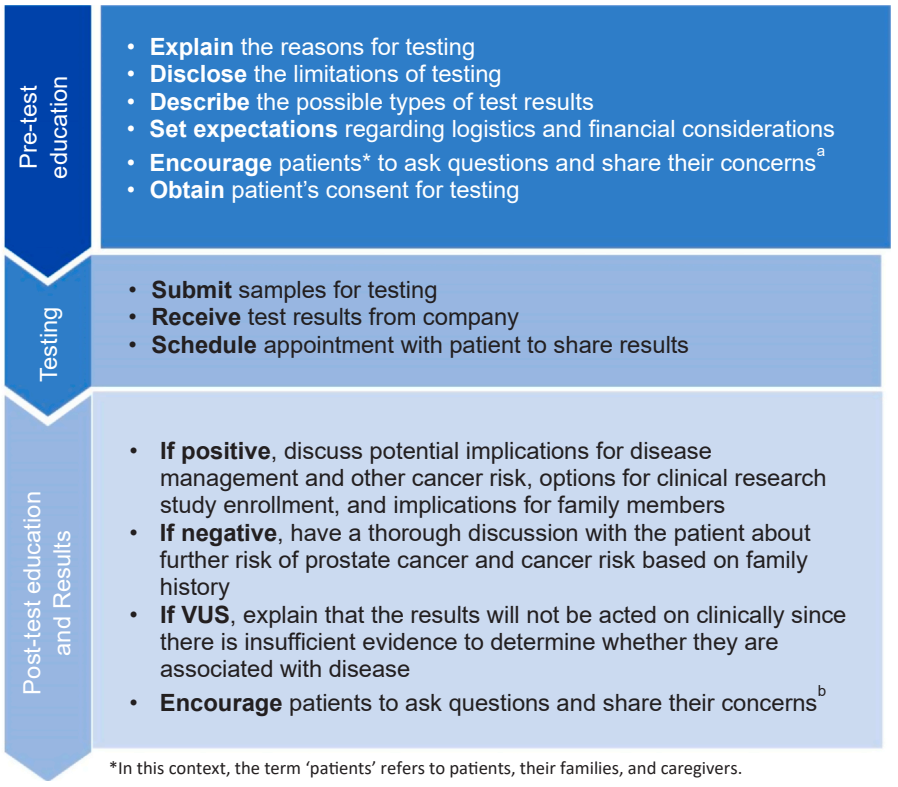

Figure 1. Practical considerations for implementing universal germline prostate cancer genetic testing.

- Germline testing results can be
  - Negative: no likely PGV identified in the genes tested
  - Positive: indicating the presence of PGV
  - VUS: Variants with insufficient evidence to determine if they are disease-causing are classified as VUS and are not clinically actionable. They may be reclassified as benign or pathogenic as more data becomes available. For example, 8.7% of VUS in one study were reclassified as pathogenic over 12 years, though most remain benign.[28] Underrepresentation of non-European groups in genomic databases increases VUS rates in these populations, and greater diversity in research will improve variant reclassification
- Discuss reclassification of variants
  - Germline VUS can be reclassified to benign or pathogenic as more information is learned about them
  - PGV can also, albeit rarely, be reclassified as VUS
- Set expectations regarding logistics
  - Discuss turnaround time for results
  - Ask patients if they want their results delivered in person, via phone, or video
- Discuss financial and legal considerations
  - The cost of testing varies and should be clearly communicated to patients, as some companies offer flat fees while others do not. Costs may also depend on whether the patient meets NCCN or insurance criteria. For those who don't (eg, Gleason 6 PCa with insufficient family history), a self-pay cost discussion is needed. Transparency ensures informed decisions, as fees can vary by lab and result in higher out-of-pocket expenses.
  - Patients may worry about genetic discrimination from insurance or employers. In the U.S., the

Table 1. Key strategies for improving efficiency during germline genetic testing.

Strategy	Details
Point of care testing	• For universal germline testing to be effective, it should be integrated into point-of-care settings with urologists, medical oncologists, radiation oncologists, and possibly informed primary care physicians. Pre-test counseling can be brief, done via video or group sessions, with referrals limited to those who test positive. Point-of-care pre-test counseling eliminates the need for post-test genetic counseling for negative results, as there's no justification for all men to see a genetic counselor when 90%-95% of them will test negative.
Telemedicine	• Use of telemedicine has proven effective in increasing access to genetic counseling by overcoming geographic and scheduling barriers. It enhances the efficiency of germline genetic testing by offering convenient, flexible counseling options without the need for in-person visits and has been shown feasible in large registries.
Role of genetic counselors	• Genetic counselors have traditionally been the point of contact with pre-test education however when volume of cases are elevated, it may be more logistically feasible for other healthcare providers to facilitate this part of testing.
Visual aids and resources	• Incorporating decision aids, emotional support tools, risk-benefit charts, and chatbots improve informed consent, enhance patient outcomes, and increase efficiency by reducing the need for extensive in-person counseling, thus allowing providers to focus on those requiring personalized care.
Test choice	• In the context of universal genetic testing, it is important to consider a gene panel that is targeted to the indication. Table 2 provides examples of prostate-specific gene panels that could be considered. Note these lists are updated often and may not be reflective of the current offering after publication.

Genetic Information Nondiscrimination Act protects against certain genetic discrimination but excludes life, disability, and long-term care insurance, and does not apply to employers with fewer than 15 employees.

- The Affordable Care Act protects against discrimination based on pre-existing conditions, including germline variants linked to cancer risk, ensuring equitable access to care and interventions.

- Encourage patients to ask questions and share their concerns (see Fig. 1)
- Obtain patient's informed consent

- A detailed consent form covering testing scope, outcomes, and privacy should be completed by the patient. A template is available in the 2024 review by Armstrong et al.[29]
- If a patient declines GGT, HCPs should respect the decision, ensure it's informed, address concerns, and document the discussion.
- Upon receipt of consent, the HCP team will select the appropriate test (Table 2), collect the necessary samples and send them to the company for testing.

- What resources are available?

- Providing patients with comprehensive resources (eg, contact information for the genetic center) and FAQs will prepare them, enabling informed decisions and optimal care (see Supplement for patient resources).
- Additional tips and workflows for clinicians

- Genetic navigators and specialized software help clinicians consistently facilitate UGGT by keeping testing top of mind, with automated reminders and workflow integration reducing the risk of oversight during busy appointments.
- Utilizing pre-test checklists like the one developed by the Canadian Association of Genetic Counselors (https://www.cagc-accg.ca/?page=470) can help support non-genetics oncology providers in during the pre-test phase.

Post-Test Education and Results

- What is it?

- Post-test education helps patients interpret results, including positive, negative, or unclear findings, while providing psychosocial support to guide personalized disease management.

- Who provides it?

- The ordering HCP can disclose and manage these results and provide the post testing education. Alternatively, patients may be informed by a letter followed by the option for post-test counseling with a genetics team.
- In general, GC should focus on post-test discussions for VUS and PGV cases, not negative GGT follow-ups unless requested, due to the high demand and limited availability of specialists. Streamlined processes are essential to address logistical challenges.

- How is it done?

- The post-test education session can be conducted in-house at medical centers or by video.
- Patients can also access post-test counseling through various avenues, including GGT companies that often provide counseling as part of their service.

Table 2. Germline genetic tests.

Ambry Genetics (USA)	– Key Test: ProstateNext – Genes tested: *ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53,* – List Price: $249
Blueprint Genetics (Finland)	– Key Test: Comprehensive Hereditary Cancer Panel – Genes tested: ATM, BRCA1, BRCA2, CHEK2, HOXB13, MSH2, MLH1, MSH6, PALB2, PMS2 – List Price: Undisclosed
Color Genomics (USA)	– Key Test: Color Hereditary Cancer Test – Genes tested: ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MSH2, MLH1, MSH6, PALB2, PMS2, TP53 – List Price: $249
Fulgent Genetics (USA)	– Key Test: Prostate Cancer Focus Panel – Genes tested: ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, TP53 – List Price: $450
GeneDx (USA)	– Key Test: GeneDx Hereditary Prostate Cancer Panel – Genes tested: ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53 – List Price: $550
Labcorp Genetics, formerly Invitae Corp (USA)	– Key Test: Invitae Hereditary Prostate Cancer Panel – Genes tested: ATM, ATR, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, GEN1, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2 – List Price: Undisclosed
Myriad Genetics (USA)	– Key Test: MyRisk Hereditary Cancer Test – Genes tested: ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D, TP53 – List Price: $249
Natera (USA)	– Key Test: Empower™ Hereditary Cancer – Genes tested: ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2 – List Price: $249
Prevention Genetics (USA)	– Key Test: Prostate Cancer Panel – Genes tested: ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53 – List Price: $990
Qiagen (Germany)	– Key Test: Therascreen BRCA1/BRCA2 – Genes tested: BRCA1, BRCA2 – List Price: Undisclosed
SOPHiA GENETICS (Switzerland, France)	– Key Test: Hereditary Cancer Solution (HCS) – Genes tested: ATM, BRCA1, BRCA2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PALB2, PMS2 – List Price: Undisclosed

- What topics should be covered?
  - The topics covered during a post-test education session depend significantly on the test results. Germline testing companies may offer GC and clinical support to help patients and HCPs interpret results and make informed decisions.
  - If the test result is positive, the discussion focuses on the benefits of the information:
    - A positive result for the presence of PGV necessitates comprehensive counseling on increased surveillance, potential preventive measures, potential implications for disease management (eg, PARPi for HRRm disease or PD-1 inhibitors), potential options for clinical research study enrollment, and implications for family.
    - Additionally, patients should be informed about potentially preventive strategies, including prophylactic surgeries or chemoprevention.
  - Discuss implications for family members
    - Discuss cascade testing implications, as variants like *BRCA2* elevate cancer risks (eg, prostate, breast, ovarian, pancreatic). Lynch syndrome genes increase risks for colon, uterine, and ovarian cancer.
    - Cascade testing provides economic benefits by lowering healthcare costs through early detection and prevention and ethical benefits by empowering at-risk individuals with vital information and reducing uncertainty-related stress.[2]
    - HIPAA permits healthcare providers to support cascade testing by encouraging patients to inform relatives, contacting relatives with consent, or communicating with their healthcare providers. Providers should review state laws to ensure compliance.

Table 3. Clinical studies that have explored germline mutations on prostate cancer outcomes.

Study	Description	Reference
BRCAAway (NCT03012321)	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects	Hussain MHK, et al, *J Clin Oncol,* 2024. 42
CheckMate 9KD (NCT03338790)	An Investigational Immunotherapy Study of Nivolumab in Combination With Rucaparib, Docetaxel, or Enzalutamide in Metastatic Castration-resistant Prostate Cancer	Fizazi K, et al. *Eur J Cancer Oxf Engl* 1990;2022(160):61–71.
GALAHAD (NCT02854436)	An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalie	Smith MR, et al. *Lancet Oncol* 2022; 23:362–373.
JAVELIN PARP Medley (NCT03330405)	Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors	Yap TA, et al*. JAMA Oncol* 2023;9:40–50
KEYNOTE-365 (NCT02861573)	Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer	Yu EY, et al. *Eur Urol* 2023;83:15–26.
MAGNITUDE (NCT03748641)	A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Participants With Metastatic Prostate Cancer	Chi KN, et al. *J Clin Oncol.* 2023;41(18):3339−3351.
MORE	Male Oncology Research and Education program for men at high risk for prostate cancer	Lorentz J, *Curr Oncol,* 2018. 25(2): 170−175.
NCT02484404 (ongoing)	Phase I/ II Study of the Anti-Programmed Death Ligand-1 Durvalumab Antibody (MEDI4736) in Combination With Olaparib and/ or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancer	Karzai F, et al. *J Immunother Cancer* 2018;6:141.
PROCLAIM (NCT05447637)	Germline Genetic Testing for Prostate Cancer Patients	Shore N, et al, *Eur Urol Oncol,* 2023. 6(5):477−483.
PROfound (NCT02987543)	Study of Olaparib (Lynparza) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer	de Bono J, et al, *N Engl J Med,* 2020. 382(22): 2091−2102
PROMISE Registry	The PROMISE Registry is a novel, prospective, germline registry that will collect long-term patient outcomes data to address current gaps in understanding resulting from recently FDA-approved treatments and updates to genetic testing recommendations for prostate cancer	Paller, CJ, et al. *Prostate*, 2024. 84(3): 292-302.
PROpel (NCT03732820)	Study on Olaparib Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer	Clarke NW, et al., *NEJM Evid,* 2022. 1(9): EVIDoa2200043.
QUEST (NCT03431350)	A Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer	Chi KN, et al. *Oncologist* 2023;28: e309–e312.
SWOG S1216	S1216, Phase III ADT+TAK-700 vs. ADT+Bicalutamide for Metastatic Prostate Cancer	Agarwal, N., et al*., J Clin Oncol,* 2022. 40(28):3301−3309.
TALAPRO-1 (NCT03148795)	A Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer	de Bono JS, et al. *Lancet Oncol* 2021;22: 1250–1264.
TALAPRO-2 (NCT03395197)	Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC	Agarwal N, et al., *Lancet*, 2023. 402(10398):291-303.
TOPARP (NCT01682772)	A Phase II Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer	Mateo J, et al. *Lancet Oncol* 2020;21:162–174.
TRITON2 (NCT02952534)	A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	Abida W, et al. *J Clin Oncol,* 2020. 38(32):3763-3772
TRITON3 (NCT02975934)	A Study of Rucaparib Versus Physician's Choice of Therapy in Participants With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	Fizazi K, et al. *N Engl J Med* 2023; 388:719–732.

- HCPs should also be prepared to help patients with positive results secure appropriate referrals for other cancer risk outside of prostate.
  - If the test result is negative, it provides reassurance to both physician and family members about the reduced risk for known hereditary cancer syndromes associated with PCa.
- Consider providing a letter to the patient with clear interpretation of the limitations to the negative result and offer a follow up call if the patient desires.
- Patients may still be at risk for cancer based on family history. If a father and sister have colon cancer for example, that patient should be getting more colon screening based on familial risk despite testing negative for the Lynch genes.
  - Encourage patients to ask questions and share their concerns (see Fig. 1).

- What resources are available?
  - Resources are available for template family letters that can be generated facilitate dialog around cascade testing. (https://www.vumc.org/geneshare/tools-share-genetic-test-results)
  - Additional resources, handouts, and recommendations are available in a 2-part review article from Armstrong et al[29] and Serritella et al.[30]

Future Outlook

Ongoing research is crucial for understanding PGV in PCa (Table 3). For example, the MORE program studies genetic factors and long-term outcomes in men with high familial risk, while the Germline PROMISE Registry, with 5000 patients, aims to identify genetic markers, improve cancer prevention, and develop personalized treatment strategies.

Limitations

This paper has inherent limitations, such as potential subjectivity and a narrower analytical focus. Additionally, this paper does not cover genetic testing for PCa risk, newer testing methodologies, the difference between germline and somatic testing, or somatic testing in depth. Despite these potential limitations, our paper provides strong insight into the concept of UGGT and provides practical guidance to complement existing published information, ensuring a distinct contribution to the field without overlap.

Conclusion

GGT is an essential component of personalized PCa care, yet its integration remains inconsistent due to multifaceted barriers, and many patients with PGV that are known to cause PCa are missed. UGGT among patients with PCa could address this problem by simplifying testing guidelines, ensuring universal coverage, and reducing the number of patients with missed testing. However, barriers to universal testing remain, including insurance coverage, access to adequate counseling services, and streamlined approaches to reduce the burden of testing. To maximize the benefits while mitigating the potential risks of UGGT, it is essential to address implementation details, including careful gene panel selection, VUS reporting and management, appropriate genetics follow-up, and seamless integration of test reports into EMRs for accessibility by patients and providers.

Ethical Declarations

Not required.

Disclosures

None.

CRediT Authorship Contribution Statement

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Declaration of Competing Interest

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Appendix A. Supporting Information

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