Philadelphia Prostate Cancer Consensus 2019: Implementation of Genetic Testing for Inherited Prostate Cancer

Editors:
Leonard G. Gomella, MD
Karen E. Knudsen, PhD, MBA
Veda N. Giri, MD
Introduction to the 2019 Philadelphia Prostate Cancer Consensus Program: “Implementation of Genetic Testing for Inherited Prostate Cancer” .................................................................1
Leonard G. Gomella, Karen E. Knudsen, Veda N. Giri

Urology perspective on the expanding world of germline testing for prostate cancer ............................................5
Michael S. Cookson

Natural history and imaging in men with high genetic risk for developing prostate cancer .........................7
William L. Dahut, Anna Couvillon, Peter A. Pinto, Baris Turkbey, Fatima Karzai

Advances in germline genetics for prostate cancer funded by the Prostate Cancer Foundation .........................9
Howard R. Soule, Andrea K. Miyahira

DNA repair genes: contributions to prostate cancer predisposition and aggressiveness .................................10
Julie Boyle, Kathleen A. Cooney

Updated insights into genetic contribution to prostate cancer predisposition: focus on HOXB13 .......................12
William B. Isaacs, Kathleen A. Cooney, Jianfeng Xu

Considerations of multigene test findings among men with prostate cancer – knowns and unknowns .........................................................14
Saud H. AlDubayan

Polygenic risk scores for prostate cancer: testing considerations .........................................................................17
Amanda Ewart Toland

Germline contributions to metastatic prostate cancer .......................................................................................19
Heather H. Cheng

The AR-DNA repair axis: insights into prostate cancer aggressiveness ............................................................22
Karen E. Knudsen

Molecular insights into the germline for prostate cancer initiation, progression, and aggressiveness ......24
Colin C. Pritchard

African American and Asian males: what do we know about germline predisposition to prostate cancer .........................................................27
Curtis A. Pettaway

Prostate cancer genetic testing: NCCN familial high-risk assessment: breast/ovarian .....................................29
Mary B. Daly
Germline testing in those at risk of prostate cancer ................................................................. 31
Peter R. Carroll, John S. Witte, J. Kellogg Parsons

Current recommendations for prostate cancer genetic testing: NCCN prostate guideline .......... 34
James L. Mohler, Celestia S. Higano, Edward M. Schaeffer, Heather H. Cheng

Current prostate cancer genetic testing capabilities and considerations ..................................... 38
Robert Pilarski

Genetic counseling considerations for men with prostate cancer .............................................. 40
Ashley H. Woodson

Alternate delivery models for genetic counseling: clinical and implementation considerations ................................................................. 42
Alanna Kulchak Rahm

Genetic education and practice considerations of non-genetic providers .................................. 44
Veda N. Giri

Considerations of germline testing in prostate cancer screening ............................................. 46
Thomas J. Polascik, Hazem Orabi on behalf of the Duke Cancer Institute
Prostate Cancer Screening Collaborative

Germline testing for prostate cancer prognosis: implications for active surveillance ............... 48
Brian T. Helfand, Jianfeng Xu

Germline testing for prostate cancer: community urology perspective ..................................... 50
Raoul S. Concepcion

Genetic counseling perspective of engagement with urology and primary care ....................... 52
Colette Hyatt, Jessica Russo, Carey McDougall

Genetically-informed treatment for advanced and metastatic prostate cancer .......................... 54
Alicia K. Morgans, Brittany M. Szymaniak

Genetic counseling and oncology: proposed approaches for collaborative care delivery .......... 57
Jacquelyn Powers, Kelsey Spielman, Rebecca Mueller, Melissa Batson, Stacy Pundock, Anna Arutyunova, Heather Symecko, Susan Domchek
Philadelphia Prostate Cancer Consensus Conference 2019: Implementation of Genetic Testing for Inherited Prostate Cancer
Sidney Kimmel Cancer Center, Thomas Jefferson University
Philadelphia, Pennsylvania
October 4-5, 2019

Agenda

Time Day 1 - October 4, 2019

11:00-12:00 ARRI VALS and REGISTRATION
Loews Hotel
12th and Market Street
Philadelphia, PA

SESSION I: OPENING SESSION
Session Chair: Dr. Leonard Gomella – Sidney Kimmel Cancer Center at Jefferson

Objectives of Session I:
• Outline consensus process and overview of 2017 consensus results
• Prioritize key areas in need of consensus from multiple disciplines
• Incorporate patient stakeholder perspective for relevance of consensus results

12:00-12:30 Opening Remarks:
• Welcome Consensus Participants: Drs. Leonard Gomella/Karen Knudsen/Veda Giri
• Acknowledgements: Supporters and Participants: Dr. Leonard Gomella – Sidney Kimmel Cancer Center at Jefferson
• Welcome to Jefferson: Mark L. Tykocinski, MD Provost and Executive Vice President for Academic Affairs, Thomas Jefferson University; The Anthony F. and Gertrude M. DePalma Dean Sidney Kimmel Medical College at Thomas Jefferson University

12:30-12:45 Overview of the Philadelphia Prostate Cancer Consensus Meeting:
Dr. Veda Giri – Sidney Kimmel Cancer Center at Jefferson
• Summary of consensus 2017
• Consensus 2019 program and process to be followed
• Endorsements to be requested from other organizations

12:45-1:00 National Urologic Perspective on the Expanding World of Germline Testing for Prostate Cancer
– Dr. Michael Cookson – University of Oklahoma; President Elect, Society of Urologic Oncology; American Urological Association

1:00-1:15 National Oncology and Clinical Trials Perspective on the Expanding World of Germline Testing for Prostate Cancer
– Dr. William Dalut – National Cancer Institute

1:15-1:30 National Cancer Genetics Perspective on the Expanding World of Germline Testing for Prostate Cancer
– Scott Weissman, MS, CGC – National Society of Genetic Counselors

1:30-1:45 Prostate Cancer Foundation: Key Perspectives on Germline Testing and Changing the Face of Lethal Prostate Cancer
– Dr. Howard Soule – Executive Vice President, Chief Science Officer, Prostate Cancer Foundation

1:45-2:00 A Patient’s Perspective on Prostate Cancer Genetic Testing
– Mr. Peter Kaye

2:00-2:15 Panel Q/A

2:15-2:30 Break
SESSION II: UPDATE OF PROSTATE CANCER GENETICS AND GENOMICS
Session Chair: Dr. Dan Lin – University of Washington

Objectives of Session II:
- Propose a prioritized list of genes for germline testing
- Propose strategy for integration of somatic testing with germline evaluation
- Propose prioritized list of genes for germline testing in diverse populations and areas in need of key research

2:30-2:40 Updated Insights into Genetic Contribution to Prostate Cancer Predisposition and Aggressiveness: Focus on BRCA1/2 and DNAMismatch Repair Genes – Dr. Kathleen Cooney – Duke University

2:40-2:50 Updated Insights into Genetic Contribution to Prostate Cancer Predisposition and Aggressiveness: Focus on HOXB13 and Other Cancer Genes – Dr. William Isaacs – Johns Hopkins University

2:50-3:00 Considerations of Multigene Test Findings Among Men with Prostate Cancer – Knowns and Unknowns – Dr. Saud AlDubayan – Dana Farber Cancer Institute

3:00-3:10 Polygenic Risk Scores: Testing Considerations – Dr. Amanda Toland – Ohio State University

3:10-3:20 Germline Contribution to Metastatic Prostate Cancer – Dr. Heather Cheng – University of Washington

3:20-3:30 Panel Q/A

3:30-3:50 Coffee Break

3:50-4:00 AR signaling and DNA Repair: Insights Into Prostate Cancer Progression and Aggressiveness – Dr. Karen Knudsen – Sidney Kimmel Cancer Center at Jefferson

4:00-4:10 Molecular Insights into the Germline for Prostate Cancer Initiation, Progression, and Aggressiveness – Dr. Colin Pritchard – University of Washington

4:10-4:20 African American And Asian Males: What Do We Know About Germline Predisposition to Prostate Cancer? – Dr. Curtis Pettaway – MD Anderson Comprehensive Cancer Center

4:20-4:30 Panel Q/A

SESSION III: NCCN PROSTATE CANCER GENETIC TESTING GUIDELINES
Session Chair: Dr. Veda Giri – Sidney Kimmel Cancer Center at Jefferson

Objectives of Session III:
- Identify consistent genetic testing criteria across guidelines
- Uncover differences in testing criteria across guidelines and propose consistency

4:30-4:45 Current Recommendations for Prostate Cancer Genetic Testing: NCCN Genetic/ Familial High-Risk Assessment: Breast and Ovarian – Dr. Mary Daly – Fox Chase Cancer Center

4:45-5:00 Current Recommendations for Prostate Cancer Genetic Testing: NCCN Prostate Cancer Early Detection – Dr. Kelly Parsons – University of California, San Francisco

5:00-5:15 Current Recommendations for Prostate Cancer Genetic Testing: NCCN Prostate Cancer Guidelines – Dr. James Mohler – Roswell Park Comprehensive Cancer Center

5:15-5:30 Panel Q/A

5:30 Adjourn

6:30-9:30 Reception, Dinner and Guest Speaker Mr. Reggie Jackson

PM Loews Hotel
Time       Day 2- October 5, 2019

7:15-8:00  Hamilton Building
Thomas Jefferson University Center City Campus
Sign in Day 2

8:00-8:15  Summary of Day 1 – Dr. Veda Giri – Sidney Kimmel Cancer Center at Jefferson

SESSION IV: PROSTATE CANCER GENETIC TESTING CAPABILITIES AND GENETIC COUNSELING
Session Chair: Dr. Richard Wender – Chief Cancer Control Officer, American Cancer Society

Objectives of Session IV:
• Define key genetic counseling elements for men with or at risk for prostate cancer
• Define what constitutes “informed consent/informed decision-making” for genetic testing
• Propose prioritized approaches to alternate delivery of genetic counseling
• Define key elements of knowledge and care for non-genetic providers performing genetic testing

8:15-8:25  Current Prostate Cancer Genetic Testing Capabilities and Considerations – Robert Pilarski, MS, LGC, MSW – Ohio State University and NCCN

8:25-8:35  Overview of Genetic Counseling: Past, Present, and Future – Annie Blanco, MS, CGC – University of California, San Francisco

8:35-8:45  Unique Considerations and Appropriate Pretest Informed Consent for Germline Testing of Men with Prostate Cancer – Ashley Woodson, MS, CGC – MD Anderson Comprehensive Cancer Center

8:45-8:55  Alternate Delivery Models for Genetic Counseling and Education: Clinical and Implementation Considerations – Dr. Alanna Rahm – Geisinger Health

8:55-9:05  Genetic Education and Practice Considerations for Non-Genetic Providers – Dr. Veda Giri – Sidney Kimmel Cancer Center at Jefferson

9:05-9:15  Current Prostate Cancer Clinical Trials in Genetic Testing, Counseling, and Education Delivery – Dr. Mary Ellen Taplin – Dana Farber Cancer Institute

9:15-9:30  Panel Q/A

9:30-9:45  Break

SESSION V: IMPLEMENTATION OF GENETIC TESTING IN UROLOGY AND PRIMARY CARE
Session Chair: Dr. Anthony Costello – Prostate Cancer Center Melbourne, Australia

Objectives of Session V:
• Propose prioritized list of genes to test to inform prostate cancer screening and active surveillance discussions
• Propose prioritized genetic counseling strategies (traditional and alternate models) to rapidly meet genetic counseling needs of men in a urology or primary care clinic setting
• Propose approaches for collaborative care delivery between urologists, primary care providers, and genetic specialists


9:55-10:05  Considerations of Germline Testing for Active Surveillance – Dr. Brian Helfand – Northshore University Health System, Chicago

10:05-10:15  Community Urology Perspective on Germline Testing for Prostate Cancer – Dr. Raoul Concepcion – Integra Connect, West Palm Beach Florida

10:15-10:25  Genetic Counseling Perspective of Engagement with Urology – Colette Hyatt, MS, LCGC – Sidney Kimmel Cancer Center at Jefferson

10:25-10:40  Panel Q/A
SESSION VI: IMPLEMENTATION OF GENETIC TESTING IN ONCOLOGY
Session Chair: Dr. Arthur “Bud” Burnett – Johns Hopkins University

Objectives of Session VI:
• Propose prioritized list of genes to test to inform treatment of men with advanced or metastatic prostate cancer
• Propose prioritized genetic counseling strategies (traditional and alternate models) to rapidly meet genetic counseling needs of men in an oncology clinic setting
• Propose approaches for collaborative care delivery between oncologists and genetic specialists

10:40-10:50 Genetically-Informed Treatment for Advanced and Metastatic Prostate Cancer – Dr. Alicia Morgans – Northwestern University, Chicago

10:50-11:00 Genetically-Informed Radiation Treatment for Prostate Cancer – Dr. Felix Feng – University of California, San Francisco

11:00-11:10 Community Oncology Perspective on Germline Testing for Prostate Cancer – Dr. Michael Mullane, Aurora Advanced Healthcare, Wisconsin

11:10-11:20 Genetic Counseling Perspective on Engagement with Oncology – Jackie Powers, MS, LCGC – University of Pennsylvania

11:20-11:30 Panel Q/A

11:30-12:15 LUNCH

12:15-3:00 Session VII: CONSENSUS TOPICS FOR DELIBERATION
Session Chairs: Drs. Leonard Gomella, Karen Knudsen, Veda Giri

Objectives of Session VII:
• Vote on a series of questions for the final consensus manuscript
• Define patient resources to be developed post-consensus
• Define provider resources to be developed post-consensus
• Identify where do we need to go in the future

Wrap Up

3:00 PM 2019 PHILADELPHIA PROSTATE CANCER CONSENSUS ENDS
Introduction to the 2019 Philadelphia Prostate Cancer Consensus Program: “Implementation of Genetic Testing for Inherited Prostate Cancer”

Leonard G. Gomella, MD, Karen E. Knudsen, PhD, MBA, Veda N. Giri, MD
Thomas Jefferson University, Sidney Kimmel Cancer Center, Philadelphia, Pennsylvania, USA

In 2017 the Sidney Kimmel Cancer Center of Thomas Jefferson University held the first international consensus conference on the role of genetic testing for inherited prostate cancer risk. This article outlines the key elements of our 2017 consensus meeting and discusses the rationale and design of our follow up 2019 Philadelphia Prostate Cancer Consensus titled the “Implementation of Genetic Testing for Inherited Prostate Cancer.”

Key Words: prostate cancer genetics, consensus conference

Prostate cancer continues to represent a major health care burden in the United States and in many other countries. Prostate cancer is recognized to be both a clinically and genetically heterogeneous disease with inherited factors accounting for significantly increased lifetime risk for the disease in certain men. Our understanding of the genetics of inherited prostate cancer is progressing rapidly. We are learning more about how these genetic results may inform all aspects of prostate cancer care from screening and diagnosis through the treatment of early stage disease to life threatening metastatic disease.

The carrier rates of germline mutations in men with metastatic prostate cancer has been reported at approximately 12%. Additional studies from cohorts of men with prostate cancer have reported rates of germline mutations of 15%-17% regardless of stage. Genetic mutations in certain genes, such as BRCA2, significantly raise the lifetime risk for prostate cancer, and some are associated with risk for aggressive disease.

To add context to how rapidly this field is expanding we can refer to recent changes in the NCCN (National Comprehensive Cancer Network) guidelines(https://www.nccn.org/professionals/physician). Before 2017, detailed genetic testing guidelines for men with prostate cancer were only found in the NCCN Hereditary Breast and Ovarian Cancer (HBOC) guidelines. For many years this section of the NCCN guidelines had...
Introduction to the 2019 Philadelphia Prostate Cancer Consensus Program: “Implementation of Genetic Testing for Inherited Prostate Cancer”

In order to bring some clarity and cohesiveness to this evolving area of genetic evaluation for inherited prostate cancer in 2017, we convened the first Philadelphia Prostate Cancer Consensus meeting. This meeting brought together a diverse multidisciplinary group to address a genetic evaluation framework for inherited prostate cancer in the multigene testing era. The panel members included over 70 stakeholders with expertise in prostate cancer early detection, treatment, genetic counseling, research, bioethics, as well as patient advocates and national organizations. The participants also included individuals with expertise in breast cancer and gynecologic oncology to provide perspectives on hereditary breast and ovarian cancer syndromes and models of genetic assessment.

The results of the 2017 consensus meeting were published in the Journal of Clinical Oncology in 2018. Some of the 2017 consensus findings included the following highlights and endorsements:

- Expansion of referral criteria to include age at diagnosis, broader family cancer history, and broader tumor sequencing results.
- Shared decision-making for genetic counseling and genetic testing for prostate cancer.
- Expansion of testing criteria to encompass hereditary cancer syndromes in which prostate cancer has been implicated.
- Genetic testing for men with metastatic castration-resistant prostate cancer.
- Expansion of genetic testing to include hereditary cancer syndromes or broader family cancer history.
- Expansion of BRCA2-informed prostate cancer screening to include consideration of age at diagnosis of prostate cancer in male blood relatives.
- Consideration of HOXB13 genetic testing and the role in prostate cancer screening.
- Inclusion of genetic information in management discussions of early-stage and advanced prostate cancer.
- Consideration of the emerging role of ATM in prostate cancer management discussions.
- Articulation of needs for expanded research on the role of genetic testing in prostate cancer for African American men, outcomes, and cost of care.

Multigene panels are now widely available for testing for inherited prostate cancer from a variety of commercial and institutional laboratories. These include genes known to contribute to prostate cancer predisposition as well as increase the risk of other related cancers such as breast (both male and female), ovarian, pancreatic, melanoma, gastrointestinal (Lynch syndrome) and others. This expanded testing capability raises the importance of tailoring genetic counseling for males and their families regarding potential findings and implications to make informed decisions for proceeding with genetic testing. Furthermore, precision medicine in the advanced and metastatic setting and precision management in the early stage setting are now driving a significant portion of genetic testing from non-genetic practices such as oncology and urology, necessitating expert consensus regarding approaches for responsible implementation of genetic testing for men with prostate cancer.

The theme of our second consensus meeting is “Implementation of Genetic Testing for Inherited Prostate Cancer.” Critical issues to be addressed by the 2019 consensus include:

1. Update of genetic evaluation framework and genes associated with prostate cancer.
2. Delivery and incorporation of genetic testing and genetic counseling for men with all stages of prostate cancer from active surveillance through treatment of metastatic castration resistant prostate cancer for urologic and oncologic practices.
3. Delivery and incorporation of genetic testing and genetic counseling for prostate cancer screening and risk assessment.
4. Approaches for cascade testing for family members of male mutation carriers.
5. Optimum strategies for the education of urologic and oncologic providers.
6. Identification of gaps, such as application of genetic testing in diverse populations (e.g., African American, others) and defining the areas for future studies.

The consensus conference will be attended by a group of US and international experts spanning across disciplines involved in prostate cancer genetics including the following areas: urologists, medical oncologists and radiation oncologists involved with prostate cancer
diagnosis and treatment, genetic counseling, basic and clinical science research, policy experts, and patients and patient advocacy representatives. We invited members of various professional groups who are stakeholders in this area of integrating genetic testing and prostate cancer care. Members invited to attend the conference are from organizations such as several NCI-designated and community cancer centers, the National Comprehensive Cancer Network (NCCN), the National Cancer Institute (NCI), the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiation Oncology (ASTRO), the American Cancer Society (ACS), the American Urological Association (AUA), the Prostate Cancer Foundation (PCF), National Society of Genetic Counselors (NSGC), Prostate Cancer International (PCI), the Prostate Conditions Education Council (PCEC), the Society of Urologic Oncology (SUO), patient advocates and other groups. Key organizations will be provided with the final consensus document as recommended by the steering committee and given the opportunity to endorse the final consensus statements prior to submission and publication. Steering Committee members are listed in Table 1.

Expert speakers were invited by the program leadership based on their expertise in this area to present information to help address the overarching consensus questions. A multidisciplinary steering committee reviewed and approved the program content.

Beginning on October 4, 2019, the consensus meeting will be conducted in a similar structure and design of the modified Delphi method as our first meeting held in Philadelphia in March 2017. A series of speakers will address different aspects of this year’s theme of “implementation of genetic testing for prostate cancer”. The final session on Saturday, October 5 will involve the participants answering a series of questions informing the best practice approach to prostate cancer genetic testing. An audience response system will be used to capture the audience responses to a series of these critical questions. After the information is gathered a final consensus manuscript will be drafted to address the questions and will be circulated to the group for final comment and approval prior to submission for publication. The choice of the journal will be selected by the conference leadership and steering committee.

### Table 1. “Implementation of Genetic Testing for Inherited Prostate Cancer” 2019 Philadelphia Prostate Cancer Consensus steering committee members.

| Chair: Dr. W. Kevin Kelly – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Michael S. Cookson – President Elect Society of Urologic Oncology (SUO). University of Oklahoma, Oklahoma City, OK |
| Dr. William L. Dahut – National Cancer Institute, Bethesda, MD |
| Dr. Adam P. Dicker – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Felix Feng – UCLA San Francisco, CA |
| Dr. Veda N. Giri – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Leonard G. Gomella – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Karen E. Knudsen – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Daniel W. Lin – University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA |
| Dr. Stephen C. Peiper – Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA |
| Dr. Daniel P. Petrylak – Yale Cancer Center, New Haven, CT |
| Mr. Robert Pilarski – Ohio State University, Columbus, OH |
| Ms. Wendy L. Poage – Executive Director Prostate Conditions Education Council (PCEC), Denver, CO |
| Mr. Michael D. Scott – Prostate Cancer International (PCI), Philadelphia, PA |
| Dr. Howard R. Soule – Prostate Cancer Foundation (PCF) Santa Monica, CA |
| Mr. Scott Weissman – National Society of Genetic Counselors, Chicago, IL |
| Dr. Richard Wender – American Cancer Society, Atlanta, GA |
Introduction to the 2019 Philadelphia Prostate Cancer Consensus Program: “Implementation of Genetic Testing for Inherited Prostate Cancer”

This second 2019 Philadelphia Prostate Cancer Consensus is being made possible by support from Jefferson’s Sidney Kimmel Cancer Center (http://www.kimmelcancercenter.org), Jefferson’s Department of Urology and through grants from a variety of pharmaceutical, reference laboratories, and other interested parties. Without their financial support this meeting would not be possible. Industry sponsors have the option for their representatives to attend the lectures and discussions as non-voting observers. The meeting was developed as a non-CME certified meeting. Current sponsorship is acknowledged elsewhere in this supplement.

This October 2019 supplement of The Canadian Journal of Urology International contains summaries of the 2019 consensus presentations. It is not meant to be a substitute for the final consensus document. Rather it provides a high-level overview of the information that will be used in the consensus panel discussions for the creation of the final consensus statements. It also provides consensus speakers, moderators and participants with pre-meeting review materials to enhance their participation. We hope that the information published herein will also be useful to a broader audience who are not participating in our consensus but are interested in this rapidly evolving field.

Disclosures

Dr. Leonard G. Gomella is on the Advisory Board for Astellas, Bayer, Clovis, Janssen, Merck and Strand Diagnostics.

Dr. Karen E. Knudsen received research support from Celgene, Sanofi, Novartis and CellCentric and on the advisory board for CellCentric, Sanofi, Celgenem Atrin, Janssen and Genentech.

Dr. Veda N. Giri has no disclosures.

References

Urology perspective on the expanding world of germline testing for prostate cancer

Michael S. Cookson, MD
Department of Urology, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA

The management of high-risk prostate cancer is evolving. Currently, most decisions are based on traditional factors such as tumor grade and stage. However, we are in a state of evolution. A new understanding of the value of both genetic and somatic germline testing is upon us. Perhaps even more exciting is the recognition that genomic testing can and should be moved up in certain high-risk patients so more effective and targeted therapy can be applied earlier in the disease state.

Key Words: prostatic neoplasm, genetic testing, germline mutations

The management of men with prostate cancer that includes high-risk localized, regional, metastatic castration sensitive prostate cancer (mCSPC) and castration resistant prostate cancer (CRPC) is evolving. Currently, most decisions are based on traditional factors such as tumor grade (Gleason), stage, volume and location of metastatic burden, response to therapy and performance status. Studies in mCSPC have reported additional survival benefit with treatment added to traditional ADT.1,2 However, even in the CRPC state clinical factors such as prior treatments, degree of symptomology, performance status, staging and location of tumor predominantly drive treatment recommendations.3 Along the way, we have begun to appreciate the predictive and potentially prognostic value of both genetic and somatic germline testing. The hope, and in some instances the reality, is that analyzing genetic alterations may help to select therapy that is more effective as first line or in the salvage setting. Perhaps even more exciting is the recognition that genomic testing can and should be moved up in certain high-risk localized disease to guide those at risk for disease progression so that more effective therapy can be applied earlier in the disease state.

As urologists and urologic oncologists, we have been aware of a hereditary basis for prostate cancer in men with newly diagnosed prostate cancer and those presenting for screening.4 We were taught to assess family history of prostate cancer, and routinely queried our patients for first and second-degree relatives with prostate cancer. Those men with a strong family history of prostate cancer were encouraged to seek genetic counseling and testing. However, we often failed to recognize the importance of asking about other malignancies and familial syndromes in prostate cancer inheritance. Now, with an increasing understanding of the genomic profile of metastatic prostate cancer, prostate cancer is increasingly being recognized as a part of other inherited syndromes including hereditary breast and ovarian syndrome (HBOS), Lynch syndrome and hereditary prostate (HPC).5 With this increasing awareness of inherited germline mutations, we have broadened our questioning to include breast, ovarian, endometrial, pancreatic, bile duct, colorectal, and urothelial cancers. We now know that 20%-25% of patients with mCRPC will harbor either homologous recombination (HR) mutations or DNA mismatch repair (MMR) gene mutations.6,7 So, now there is an even greater emphasis on obtaining genomic testing on tissue in men with mCRPC.

What are the goals of genetic testing in men with prostate cancer? When should testing be considered? The answer is not a “one size fits all” approach. For men contemplating prostate cancer screening, the goal could be to assess an individual’s increased risk or probability above the general population for developing the disease. Patient and family members at increased risk may also elect for earlier or more aggressive screening. Further, they may also seek to modify behavior or environmental exposures in hopes of delaying or preventing the disease. Genetic and germline testing may also have an impact on prognosis. This could affect treatment selection in situations where certain therapeutics may be more or less effective in the setting of specific mutations. Recently, it was reported that intraductal carcinoma (IDCP) and invasive adenocarcinoma are BRCA2-mutant tumors.
that can arise from the same ancestral clone, implying that a temporal evolutionary trajectory exists. Functional studies have shown that BRCA2-mutant tumors may contain a subpopulation of cancer cells that can tolerate castration de novo, enabling the tumor to evade ADT therapy. So, for localized patients with this variant they might be better served with surgery as compared to radiation therapy that would normally be combined with ADT. Thus, this molecular profiling may alter treatment recommendations in the case of IDC and other subtypes.

Targeted therapy may be suitable for some men with identified pathogenic variants in specific genes. Examples of this are already being seen in some men with mCRPC who have failed first line therapy. A recent study found that patients with mCRPC with DNA repair abnormalities in the tumor have better response and an overall survival (OS) benefit when treated with poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibition with olaparib. Preliminary results of the TRITON-2 study in men with mCRPC who have failed at least one line of androgen receptor-directed therapy and one prior line of taxane-based chemotherapy reported patients with the BRCA1 or 2 mutation responded to rucaparib, whereas other patients, including those with other gene mutations like ATM and CDK12, did not respond. In another study, mCRPC patients who are BRCA2 carriers also demonstrate a 75% PSA response to carboplatin versus 17% in noncarriers. These examples demonstrate how genomic information can help identify patients for treatment and hold promise for more effective personalized medicine.

Currently, guidelines for genetic testing in patients at high risk for developing prostate cancer as well as those with an established diagnosis are evolving. Recently, the updated 2019 National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer reflect the growing importance of “genetic testing and genomically-informed disease management into clinically practice” in the management of men with prostate cancer. They recommend consideration of tumor testing for HR mutations and microsatellite instability or deficient MMR (dMMR) among patients with either regional spread or metastatic prostate cancer.

The NCCN also recommends testing for germline mutations in all newly diagnosed men with NCCN high-risk, very high-risk, regional or metastatic prostate cancer, as these men may harbor germline mutations at a higher rate than the general population. Currently, within the Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline (2017), it states, “Clinicians may consider referral for genetic counseling for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (e.g., breast, ovarian, pancreatic, other gastrointestinal tumors, lymphoma).” In addition, it is highly anticipated that a position statement or Guideline by either the American Urologic Association or the Society of Urologic Oncology addressing the role of genetic testing in prostate cancer will be forthcoming in the near future.

Disclosures

Dr Michael S. Cookson is a consultant for Myovant Sciences and Astellas Pharma US. He is on the advisory board for Janssen Scientific Affairs, Bayer Healthcare and Ferring Pharmaceuticals.

References

Natural history and imaging in men with high genetic risk for developing prostate cancer

William L. Dahut, MD,1 Anna Couvillon, CRNP,1 Peter A. Pinto, MD,2 Baris Turkbey, MD,3 Fatima Karzai, MD1
1Genitourinary Malignancies Branch, National Cancer Institute, NIH, Bethesda, Maryland, USA
2Urologic Oncology Branch, National Cancer Institute, NIH, Bethesda, Maryland, USA
3Molecular Imaging Program, National Cancer Institute, NIH, Bethesda, Maryland, USA


Introduction

Prostate cancer is the most common malignancy and the second leading cause of death in men in the United States. In 2019, an estimated 174,650 new cases were diagnosed and an estimated 31,620 men die from the disease.1 As such, established risk factors, particularly genetic contribution to prostate cancer risk, are of particular importance. An evolving approach to prostate cancer screening is to target populations of men at risk of developing prostate cancer based on known germline or likely pathogenic variants. Genome-wide association studies (GWAS) have provided evidence of genetic predisposition to the disease.2,3 Factors which contributed to this genetic predisposition include 1) early onset of disease (age ≤ 55 years); 2) multiple first-degree relatives with prostate cancer; and 3) prostate cancer with a family history of other cancers including breast, ovarian or pancreatic. GWAS studies and linkage analyses have identified several genes and chromosomal regions associated with prostate cancer. Pathogenic variants in genes such as BRCA1 and BRCA2 and HOXB13 confer modest to high lifetime risk of prostate cancer.4-6 There is also evidence of the link between prostate cancer and DNA mismatch repair (MMR) gene variants associated with Lynch syndrome.7

Recommendations for genetic counseling referrals are based on prostate cancer age at diagnosis, stage, and specific family cancer history patterns.

The IMPACT study (Identification of Men with genetic predisposition to Prostate Cancer: Targeted screening in BRCA1/2 mutation carriers and controls) is evaluating the role of targeted prostate-specific antigen (PSA) screening in men with BRCA1/2 variants.8 Preliminary results support the use of targeted PSA screening and show that screening yields a high proportion of aggressive disease. These rates are based on non-image guided biopsies and may underestimate the true prevalence of disease in these high-risk patients.

Magnetic resonance imaging (MRI) of the prostate is an emerging method for detection and diagnosis of prostate cancer. Multiparametric MRI (mpMRI) has shown advantages in detection and characterization of prostate cancer. MpMRI and MRI-targeted fusion biopsies have the potential to assist clinical decision-making and recent studies have reported mpMRI as a useful modality for predicting pathological outcomes in participants with high-risk prostate cancer.9 However, little is known about the role of mpMRI in high-risk participants as a tool for monitoring disease progression which remains to be further investigated.

In this study, we identify this targeted, high-risk population and follow the natural history of these men with known germline variants that put them at risk for developing prostate cancer. A practical approach...
to prostate cancer screening for men is taken with a documented pathogenic/likely pathogenic germline variant in a known/suspected high-penetrance cancer predisposition gene (ie: BRCA1/2).

Materials and methods

Participants are men between the ages of 30-75 years old, who must have documented germline or likely pathogenic variants in prostate cancer-related risk gene(s): BRCA1/2, MMR genes associated with Lynch syndrome (MLH1, MSH2, MSH6, PMS2, and EPCAM), HOXB13, ATM, NBN, TP53, CHEK2, PALB2, RAD51D, or FANCA). Up to 500 participants will be enrolled and all patients are initially evaluated with a complete history and physical and family history questionnaire. Participating investigators and sites include Dr. Heather Cheng at the University of Washington and Fred Hutchinson Cancer Research Center, Dr. Todd Morgan at the University of Michigan Medical School, and Dr. Veda Giri at the Sidney Kimmel Cancer Center at Thomas Jefferson University. Study schema is shown in Figure 1. Blood sampling for PSA and digital rectal exam (DRE) are performed and participants undergo a baseline mpMRI evaluation with follow up scans every 2 years as clinically indicated. Following initial evaluation, participants will be followed as clinically indicated, at 12 month intervals, to determine PSA level, prostate cancer treatment (if relevant), and/or disease/survival status until death. The indication for prostate biopsies may include: abnormal DRE, PSA > 2.0 ng/mL or > 2.5 ng/mL for ages 30-49 and 50-70 years respectively, Prostate Imaging-Reporting and Diagnosis System (PIRADS) 3+ MRI lesion(s) or clinical discretion. If a biopsy is indicated, an extended mpMRI-transrectal ultrasound guided biopsy will be performed as per standard procedures. The primary objective of the study is to follow the natural history of men with known germline pathogenic or likely pathogenic variants that put them at risk for developing prostate cancer. Secondary objectives include utilizing mpMRI for the localization and detection of local prostate cancer and examining the role of mpMRI in monitoring participants on active surveillance and as a tool for monitoring local disease progression. PSA, MRI, and biopsy data including stage and Gleason score obtained over time will be recorded and reported descriptively. Multiple correlative studies for research are collected including analyses on biopsy specimens, circulating cell-free DNA, plasma biomarkers, serum biomarkers, and peripheral blood mononuclear cells (PBMCs). PBMCs will be used for future retrospective biomarker validation studies.

Disclosures

The authors have no disclosures.

References

Advances in germline genetics for prostate cancer funded by the Prostate Cancer Foundation

Howard R. Soule, PhD, Andrea K. Miyahira, PhD
Prostate Cancer Foundation, Santa Monica, California, USA


The Prostate Cancer Foundation (PCF) is the world’s largest non-profit organization that funds patient-centric prostate cancer research. PCF has funded numerous critical studies surrounding the identification, biology, and clinical significance of prostate cancer germline and somatic genetic alterations, and is accelerating the application of these findings to improving outcomes for patients and their families.

Key Words: prostate cancer, genetics, research

The Prostate Cancer Foundation (PCF) is the world’s largest non-profit organization that funds patient-centric prostate cancer research. Seminal advances leading to the identification, biology, and clinical significance of prostate cancer germline and somatic genetic alterations affecting risk, malignant transformation, disease progression, tumoral sensitivity and resistance to treatments, and the ushering in of the precision medicine era have been funded by PCF. The International PCF Prostate Cancer Dream Team published landmark studies describing the landscape of germline and somatic alterations in patients with advanced prostate cancer.\textsuperscript{1,2} The significance of alterations in androgen receptor, PI3Kinase, WNT signaling genes, DNA damage repair (DDR) genes and many more were discovered in PCF-funded science projects.\textsuperscript{1,2} PCF Young Investigator Awards have supported the conduct of important clinical trials, including the GENTleMEN Study, a nation-wide study providing access for patients with metastatic prostate cancer to genetic counseling and testing, and PROREPAIR-B, the first prospective study to evaluate the impact of germline alterations in DDR genes on the outcomes of men with metastatic castration-resistant prostate cancer (mCRPC).\textsuperscript{3} One of the most important new studies funded by PCF include the TARGET study, which aims to develop mobile and web-based tools to educate physicians, patients and the public on prostate cancer genetics and facilitate timely identification of men with prostate cancer who meet NCCN guidelines for genetic testing. PCF has funded numerous other critical previous and ongoing laboratory and clinical studies in prostate cancer germline genetics, and is accelerating the application of these findings to improving outcomes for patients and their families.

Disclosures

Dr. Howard R. Soule and Dr. Andrea K. Miyahira have no disclosures.

References

DNA repair genes: contributions to prostate cancer predisposition and aggressiveness

Julie Boyle, MS,1 Kathleen A. Cooney, MD2
1Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA
2Department of Medicine, Duke Cancer Institute, Durham North Carolina, USA

INTRODUCTION

Prostate cancer exhibits a high degree of heritability which is more significant than observed in other common cancers including breast, ovarian and colon cancer.1 With the exception of the discovery of HOXB13,2 however, it has been difficult to identify rare prostate cancer susceptibility genes using genetic linkage approaches. Since DNA repair genes play a key role in maintaining genomic integrity and are known to segregate with other heritable cancers, they are strong candidates for prostate cancer susceptibility. Recently, studies of men with metastatic prostate cancer have led to the recognition that germline mutations in DNA repair/recombination genes (BRCA1/2, ATM, etc.) may occur in ~10% of men with advanced prostate cancer.3,4 Robinson et al.3 initially reported integrative tumor sequencing data from 150 men with castrate-resistant prostate cancer and identified DNA repair/recombination gene alterations in 23% of cases, with the majority harboring biallelic alterations. Notably, 13/150 (8.7%) of patients carried a pathogenic germline mutation in BRCA1/2 or ATM. A larger multisite study of 692 men with metastatic prostate cancer found an even higher rate of germline mutations (11.8%) across 20 DNA repair genes.5 Family history information was available for 88% of the patients in this study and, interestingly, men harboring a pathogenic germline mutation were more likely to have a first degree relative with prostate cancer (71%) than a first degree relative with prostate cancer (22%). These reports shed new light on the relationship of DNA repair mutation carrier status and prostate cancer risk which will be reviewed in this presentation.

Hereditary breast and ovarian cancer (HBOC) families

Early studies of HBOC families demonstrated an increased risk of prostate cancer in male mutation carriers compared to non-mutation carriers. Deleterious germline mutations in both BRCA1/2, classically associated with HBOC, have been shown to increase the risk6 and aggressiveness7 of prostate cancer, with prostate cancer risk elevated more in HBOC families with BRCA2 mutations than those with BRCA1 mutations (data from the Breast Cancer Linkage Consortium).8,9 These findings may have important prognostic and therapeutic implications for prostate cancer patients and men in HBOC families. However, it is important to note that studies of prostate cancer-only families have not found a significant number of BRCA1/2 pathogenic mutations, indicating these mutations likely contribute to a small portion of hereditary prostate cancer.

Lynch syndrome families (LS)

In addition to colorectal cancer, there are a number of cancers that occur with increased frequency in individuals carrying a pathogenic germline mutation in an LS-associated mismatch repair (MMR) gene. These LS-associated cancers occur in the endometrium, ovary, stomach, small bowel and ureter, but data supporting an LS-prostate cancer correlation has been conflicting. In 2014, Raymond et al.10 reported an overall hazard
ratio for prostate cancer of 1.99 (95% CI, 1.34 to 4.59, \( p = 0.0038 \)) across two large familial LS cancer registries, while an independent meta-analysis identified a risk elevation of 2.28-fold (95% CI, 2.32-6.67) for men with MMR mutations in LS families.11 Interestingly, prostate cancer tumors sequenced from individuals with LS carry classic microsatellite instability signatures, an uncommon observation in prostate cancer.12 In light of this new information, there is general consensus among experts that men harboring MMR mutations are at an increased risk for prostate cancer, but the magnitude of the risk elevation is not fully defined.

DNA repair genes and prostate cancer clinical attributes

Initial clinical reports with small cohort sizes suggested that prostate cancer patients harboring a BRCA1/2 deleterious mutation may experience more aggressive forms of prostate cancer leading to poor clinical outcomes.13,14 Castro et al published a report comparing clinical presentations and outcomes of 18 BRCA1 and 61 BRCA2 carriers with prostate cancer compared to 1,940 noncarriers with prostate cancer. Men carrying a deleterious BRCA1/2 mutation were more likely to have high grade (Gleason score > 8) and/or high stage (T3/T4 / N+ / M+) cancers, as well as experience shorter overall survival. Using a retrospective case: case study, Na et al15 compared the frequency of BRCA1/2 and ATM mutations between 313 men with lethal prostate cancer and 486 men with indolent prostate cancer from three distinct racial/ ethnic groups. The overall mutation carrier rate was significantly elevated in the lethal prostate cancer cohort compared to the indolent prostate cancer cohort (6.07% versus 1.44%; \( p = 0.007 \)). Additionally, BRCA1/2 and ATM mutation carrier status was an independent predictor for prostate cancer-caused death in an adjusted model. Clinically, pathogenic DNA repair mutation carrier status has been shown to confer preferential response to platinum-containing regimens16 and PARP inhibitors.17

Conclusions and future directions

In summary, pathogenic germline mutations in DNA repair genes, including BRCA1/2 and ATM, increase the risk of prostate cancer development and clinically aggressive prostate cancer phenotypes. Identification of these mutations in prostate cancer patients has clinical and therapeutic implications, as patient outcomes improve with molecularly-informed treatment approaches. Among the many areas for future investigation, gaining a better understanding of optimal approaches for early stage prostate cancer detection in male pathogenic mutation carriers and pursuing further exploration of customized post-diagnosis treatment strategies are critical.

Disclosures

Julie Boyle has no disclosures.

Dr. Kathleen A. Cooney has ownership interest in a patent on HOXB13 as a genetic marker of prostate cancer risk, owned by Johns Hopkins and University of Michigan.

References

Updated insights into genetic contribution to prostate cancer predisposition: focus on HOXB13

William B. Isaacs, PhD,1 Kathleen A. Cooney, MD,2 Jianfeng Xu, MD, Dr.PH3

1Brady Urological Institute, Johns Hopkins University, School Medicine, Baltimore, Maryland, USA
2Duke University School of Medicine and Duke Cancer Institute, Durham, North Carolina, USA
3Program for Personalized Cancer Care, NorthShore University HealthSystem, Evanston, Illinois, USA


Factors affecting the frequency of HOXB13 mutations in different prostate cancer populations will be reviewed. A number of these factors are relevant for prostate cancer susceptibility genes in general.

Key Words: high penetrance genes, prostate cancer, germline

In early 2012 the identification of the first bona fide prostate cancer-specific susceptibility gene, HOXB13 was reported.1 Using linkage analyses in prostate cancer families, a recurrent but rare missense change, G84E, was identified in the HOXB13 gene on 17q21. In an analysis of germline DNA from over 5,000 prostate cancer cases and controls, we found that the frequency of G84E was significantly higher in cases (1.4%) than controls (0.1%-0.4%). An enrichment of G84E was found in prostate cancer patients who were diagnosed at early age (eg, under 55) and with a positive family history of prostate cancer. These finding have been consistently confirmed by many labs around the world, with ORs for prostate cancer varying from 2-15 fold. Through combined analyses of different study populations in the International Consortium for Prostate Cancer Genetics (ICPCG), the observation was made that the most common mutation in HOXB13 in US men, G84E, had the highest frequency in individuals of Nordic descent.2 Indeed, as many as 8%-10% of Swedish3 and Finnish4 men with family history positive prostate cancer diagnosed at an early age carry a G84E HOXB13 mutation, compared to ~1% or less in unaffected men. A critical additional finding was that all G84E mutation carriers shared a common haplotype,2 i.e., they are all descended from a common founder, presumably of Swedish or Finnish origin. Founder mutations in HOXB13 have been found to be associated with prostate cancer risk in other populations, including G132E in Japanese men,5 and G135E in Chinese men.6 Each of these mutations, substituting a glutamic acid for glycine at amino acid positions 84, 132, and 135, respectively, lie in one of two highly conserved domains in the HOXB13 protein which are responsible for binding to the homeobox cofactor, MEIS,7,8 suggesting an alteration of this binding as a mechanistic feature of the cancer promoting action of these G to E variants.
Observations characterizing HOXB13 and its role in prostate carcinogenesis include:

1. **HOXB13 expression is highly prostate specific where it is necessary for normal prostate development.** This expression is maintained throughout initiation and progression of prostate cancer.
2. **HOXB13 interacts with AR to modulate the expression of various androgen responsive genes.**
3. As indicated above, three critical factors affect the frequency, and thus importance of G84E as a susceptibility gene:
   a. **Age of diagnosis:** men diagnosed under age 55 have the highest frequency of G84E. In men diagnosed over age 70, the frequency is not significantly different from the general population. This earlier age of onset associated with this mutation is similar to that seen in other cancers that are due to germline variants, eg, BRCA1 and breast cancer, and APC and colorectal cancer.
   b. **Family history:** the frequency of G84E is elevated in men with first degree relatives affected with prostate cancer and is highest in men diagnosed both at an early age and with a family history of prostate cancer.
   c. **Ancestry:** individuals of Swedish and Finnish ancestry have the highest population frequencies of G84E due to a founder mutation; in men of African and eastern European descent, G84E is extremely rare. Other HOXB13 founder mutations are important in Chinese and Japanese, and possibly others yet to be found.
4. While not completely consistent, most studies of clinicopathologic variables do not find any differences in prostate cancer between carriers and noncarriers of G84E. What is clear is that the association of G84E and prostate cancer is equally strong in men with high- and low-risk prostate cancer, i.e. carriers of G84E are at increased risk of the full spectrum of prostate cancer, including high risk, lethal disease.
5. **G84E can be highly penetrant:** the penetrance of G84E varies with ancestry, age at diagnosis, family history, and year of birth. Estimates range from 40% to 60% by age 85, and almost complete penetrance in men who have a strong family history of early onset prostate cancer. 6. **Penetrance of G84E may also be modified by genetic risk score (GRS) derived from multiple prostate cancer risk-associated SNPs.** In a large Swedish population-based study, the cumulative prostate cancer risk by age 80 years was 33% for G84E carriers. This risk increased to 48% if carriers also had higher polygenic risk score (top quartile). With respect to these last features of HOXB13, the G84E variant is reminiscent of more common prostate cancer risk SNPs. While most of these latter variants have a much smaller effect size on risk and are more common than G84E, they apparently share with G84E a strict association with prostate cancer initiation, not progression. Thus, the most useful application of G84E, as with the set of prostate cancer risk SNPs and GRS, is in early identification men at elevated risk for prostate cancer diagnosis, with subsequent early and more intense disease screening to detect (or prevent) clinically significant cancers at a time when they are still curable.

**Disclosures**

Dr. William B. Isaacs and Kathleen A. Cooney have ownership interest in a patent on HOXB13 as a genetic marker of prostate cancer risk, owned by Johns Hopkins and University of Michigan.

Dr. Jianfeng Xu has no disclosures.

---

**References**

Considerations of multigene test findings among men with prostate cancer – knowns and unknowns

Saud H. AlDubayan, MD1,2
1Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA
2Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts, USA

Germline genetic testing has become an increasingly informative tool in the management of cancer patients. Over the past few years, the landscape of germline testing of prostate cancer patients has evolved significantly with the introduction of several multi-gene panel tests. Here, we dissect the clinically available prostate cancer-specific multi-gene panels and explore their performance on clinical series of prostate cancer patients from different ethnic groups.

Key Words: cancer predisposition, clinical germline genetic testing, hereditary prostate cancer

Introduction

Clinical germline testing has become an increasingly useful tool guiding the clinical management of prostate cancer patients.1 Alterations in several genes, such as BRCA1, BRCA2, and the DNA mismatch repair (MMR) genes, have been associated with a large or moderate increase in the risk of developing prostate cancer where preventive measures could be implemented.2 Furthermore, pathogenic germline alterations in BRCA2 and other DNA repair genes have predictive utility for disease progression as well as patient’s response to targeted therapeutics such as poly (ADP-ribose) polymerase inhibitors (PARPi) and immune checkpoint blockades.3,4 As such, prostate cancer-specific clinical germline multi-gene panels (MGPs) have evolved substantially over the past few years. Here, we explore the current landscape of clinical MGP testing for hereditary prostate cancer and examine the prevalence of germline cancer gene alterations in prostate cancer patients who underwent clinical testing.

Materials and methods

Clinical germline MGP tests that are specifically designed for PC patients and reported in the Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) were systematically evaluated. We also conducted a literature review to assess the prevalence of pathogenic germline variants in clinical cohorts reported between January 2017 and August 2019.

Results and discussion

The number of clinical prostate cancer-specific MGPs grew from 3 in 20172 to at least 10 panels that can be currently ordered in the United States. The median number of genes in these panels is 12 (range: 4-16). All panels appropriately included BRCA1 and BRCA2. However, while all panels included NBN, CHEK2, and TP53, which either only had emerging or insufficient evidence as prostate cancer risk genes, 20% of these MGPs did not test the DNA MMR genes or HOXB13 which are established prostate cancer susceptibility genes,2 Figure 1. Notably, DNA repair genes (DRGs) (such as PALB2 and RAD51D), where germline pathogenic variants can influence treatment decisions, were only tested in 50% of the panels, highlighting an area for potential further improvement.
In a cohort of 3,607 prostate cancer patients, who underwent clinical testing using a 14-gene panel (62%, n = 2,250) or a custom clinician-selected MGP (38%, n = 1,357), 17.2% (95% CI:16.0-18.4) had pathogenic cancer predisposition variants. However, only 8.2% (95% CI:7.3-9.1) of all tested patients had pathogenic variants in prostate cancer predisposition genes with high- or moderate-grade evidence (BRCA1, BRCA2, HOXB13, and the MMR genes) while another 2.1% (95% CI:1.6-2.5) had pathogenic variants in genes with emerging evidence for prostate cancer susceptibility (ATM and NBN) totaling to 10.3% (95% CI: 9.3-11.2) of prostate cancer patients with informative results for prostate cancer risk management, Table 1. Additionally, 3.4% (95% CI:2.8-3.9) patients had pathogenic variants in CHEK2, PALB2, RAD51C, or RAD51D which have prognostic and/or therapeutic predictive utility in prostate cancer, highlighting a nontrivial subset of prostate cancer patients who may not have an identifiable prostate cancer predisposition variant but can potentially benefit markedly from clinical germline sequencing.

Collectively, around 13.6% (95% CI:12.5-14.7) of prostate cancer patients in this clinical cohort received an informative result for prostate cancer risk or treatment, which is similar to the reported prevalence of germline alterations in metastatic prostate cancer patients. Importantly, caution should be exercised when interpreting these results given the high-risk nature of this cohort and the significant heterogeneity of the clinical features and ancestral background of the tested patients. For example, only 8.4% of African American and 5.1% of Hispanic prostate cancer patients received a pathogenic variant in 

**Table 1. Prevalence of germline pathogenic variants in the established prostate cancer-risk gene set (BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, and HOXB13), genes with emerging evidence supporting their contribution to prostate cancer susceptibility (ATM and NBN), and genes with predicative utility in prostate cancer (CHEK2, PALB2, RAD51C, and RAD51D) across ancestral groups studied by Nicolosi et al.**

<table>
<thead>
<tr>
<th>Ancestral groups</th>
<th>Established PC Risk genes</th>
<th>Genes with emerging evidence for PC predisposition</th>
<th>Genes with prognostic and/or therapeutic predictive utility</th>
<th>All PC relevant genes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathogenic variants (n)</td>
<td>(%) Pathogenic variants (n) (%)</td>
<td>Pathogenic variants (n) (%) Pathogenic variants (n) (%) Pathogenic variants (n) (%)</td>
<td></td>
</tr>
<tr>
<td>White (n = 2594)</td>
<td>212</td>
<td>8.2 58 2.2</td>
<td>94 3.6 14.0</td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish (n = 234)</td>
<td>25</td>
<td>10.7 7 3.0</td>
<td>9 3.8 41</td>
<td></td>
</tr>
<tr>
<td>Black/African American (n = 227)</td>
<td>13</td>
<td>5.7 2 0.9</td>
<td>4 1.8 19</td>
<td></td>
</tr>
<tr>
<td>Hispanic (n = 78)</td>
<td>4</td>
<td>5.1 0 0.0</td>
<td>0 0.0 4</td>
<td></td>
</tr>
<tr>
<td>Asian (n = 73)</td>
<td>7</td>
<td>9.6 2 2.7</td>
<td>1 1.4 10</td>
<td></td>
</tr>
<tr>
<td>Other (n = 401)</td>
<td>34</td>
<td>8.5 6 1.5</td>
<td>13 3.2 53</td>
<td></td>
</tr>
<tr>
<td>All examined patients</td>
<td>295</td>
<td>8.2 75 2.1</td>
<td>121 3.4 491</td>
<td></td>
</tr>
</tbody>
</table>

© The Canadian Journal of Urology™: International Supplement, October 2019
Considerations of multigene test findings among men with prostate cancer – knowns and unknowns

patients had a positive test, Table 1, significantly lower than European and Ashkenazi Jewish prostate cancer patients (14.0% and 17.5% respectively). Similar results were also seen in another case series where none of 89 African American patients with localized prostate cancer had pathogenic variants in BRCA1, BRCA2, or ATM compared with 1.7% (7/352) of European patients. Conversely, a relatively high diagnostic yield was seen in Asian prostate cancer patients where 13.7% had a positive result, Table 1. Similarly, 18.18% of Asian patients with lethal prostate cancer were found by Na et al. to carry pathogenic variants in BRCA1, BRCA2, or ATM. Such variability in test performance highlights the current gaps in our understanding of the major prostate cancer risk drivers in non-European populations and the great need to study such underrepresented groups.

Conclusion

In summary, clinical germline testing of prostate cancer patients, using MGPs, has become widely available. While most MGPs include the established prostate cancer risk genes, more emphasis should be made to include genes where mutations have prognostic or therapeutic utility, Table 1. Test performance across ancestry groups should be taken into consideration when ordering MGPs on non-European prostate cancer patients. Finally, several patients had pathogenic variants in genes of unknown clinical relevance to prostate cancer, representing a significant challenge for counseling but also an opportunity to prioritize these genes in future case-control association studies.

Disclosures

Dr. Saud H. AlDubayan has no disclosures.

References

Polygenic risk scores for prostate cancer: testing considerations

Amanda Ewart Toland, PhD

Department of Cancer Biology and Genetics and Division of Human Genetics, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio, USA


Genome-wide association studies (GWAS) have identified more than 170 single nucleotide variants (SNVs) associated with prostate cancer risk. Each variant is associated with only small increases in risk and is not predictive of an individuals' overall risk of developing prostate cancer.

Numerous genome-wide association studies (GWAS) have been performed for prostate cancer leading to the discovery of over 170 single nucleotide variants (SNVs) showing modest contributions to prostate cancer risk.1-3 Currently these variants are estimated to explain 28%-33% of the familial risk of prostate cancer.1,2 Although these variants are not predictive for risk on their own, polygenic risk scores (PRS) combining risk for many SNVs are showing promise for stratifying individuals well-above average population risk as well as below population risk. One study using a model of 72 SNVs in 1725 cases and 1415 controls found that men in the top decile of PRS have a lifetime risk of prostate cancer of about 30% and men in the top 1% have up to a 42% lifetime risk.4 Another study of 147 SNVs found that the relative risk for men with the top 1% of the PRS was 5.7-fold higher than men in the middle 25%-75%.2

PRS may help to explain prostate cancer diagnoses in men with high-probability of carrying a high to moderately penetrant pathogenic variant who test negative on clinical panels for known prostate cancer genes. PRS may also be useful in decreasing overdiagnosis of prostate cancer, specifically by improving the predictive value of prostate-specific antigen (PSA) testing. A study by the PRACTICAL and UK ProtecT consortia tested a 54 SNV model in discovery and validation sets of over 21,000 prostate cancer cases, 17,500 controls and 8900 men with high PSA levels.5 This study showed that the positive predictive value for PSA testing for aggressive prostate cancer was ~25% for individuals in the highest 5% of genetic risk, compared to ~16% for individuals in the middle 50% of risk and less than 8% in individuals in the lowest 20% of risk. PRS in this study was more predictive of prostate cancer risk than family history. Inclusion of cancer family history did not improve predictive value, but in this and other studies family history further modifies absolute risk.5,6 Another population-based study found that among individuals with elevated PSA there was over a two-fold increase in the incidence of prostate cancer for those in the top PRS decile compared to those in the middle deciles.7 Collectively, these studies suggest the value of PRS in improving predictive value of family history and PSA, known risk factors for prostate cancer.

Although the majority of GWAS and PRS studies for prostate cancer have been done in European populations, a few studies evaluated the utility of PRS in other racial and/or ethnic groups.3 The majority (68%-83%) of SNVs studied show similar directional effects in East Asians, Latinos, and African Americans relative to Europeans. Although the PRS in these populations showed significant fold differences (e.g. 3-fold) between the top 10% and average risk (25%-75%) groups, the overall p values were lower.8,9

Key Words: polygenic risk score, prostate cancer, risk prediction, genome-wide association study

© The Canadian Journal of Urology™; International Supplement, October 2019
Polygenic risk scores for prostate cancer: testing considerations

Further research on the predictive value of PRS in non-European populations is critically important in order to provide equal access to predictive genetic testing.

Only one commercial company currently offers clinical PRS for prostate cancer. Criteria for testing includes male sex, European ancestry and being negative for a personal or family history of a pathogenic variant in one of 14 moderate-high risk prostate cancer-associated genes. Clinical testing reports provide an estimated lifetime risk of prostate cancer compared to the general population risk of 10.2%. A limitation of this test is that the PRS model is not combined with family history, PSA or other known risk factors to provide a more comprehensive assessment of risk.

There are multiple ways in which prostate cancer PRS could be used clinically including risk stratification for making personalized screening recommendations (alone or in a model with other risk factors), as part of national screening guidelines, to provide more refined risk estimates for individuals with a pathogenic high-risk variant, and for prognostic information in individuals with elevated PSA. Future clinical applications may include PRS for prediction of radiation side effects after prostate cancer treatment.1 PRA may also have utility for some patients who are already undergoing genetic testing for high-risk genes in helping them to understand why they developed prostate cancer.

Despite the promise of clinical utility of prostate cancer PRS, there are a significant number of gaps in our knowledge. Most critical are our limited understanding of their predictive value, especially in non-European populations, how much models may change with additional genetic information, what other risk factors should be included, what predictive value is needed for clinical use, the accuracy of PRS across different age groups, whether PRS can be used to predict “when” an individual’s risk crosses a screening threshold, if PRS impacts outcomes, how to present the information to patients, and how to train providers to understand and appropriately use this information. On-going clinical trials are determining if PRS are useful biomarkers for screening. As PRS for prostate cancer become more widely available clinically, additional studies are needed before routine use of PRS for prognosis and screening strategies.

Disclosures

Dr. Amanda Toland has no disclosures.

References

Germline contributions to metastatic prostate cancer

Heather H. Cheng, MD, PhD1,2
1Department of Medicine, University of Washington, Seattle, Washington, USA
2Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA


Recent studies demonstrate that the prevalence of germline mutations in DNA repair genes in metastatic prostate cancer is higher than previously recognized, and is higher than in localized disease and in unaffected men. This is compelling evidence that specific gene dysfunction is critical in prostate cancer initiation and/or evolution to metastases. Applications to treatment in advanced disease are imminent, and further investigation in early-stage disease, as well as in diverse and at-risk populations will help maximize clinical benefit.

Key Words: BRCA2, BRCA1, prostate cancer, cancer predisposition, DNA repair, germline, metastases

Introduction

Prostate cancer is recognized to have a heritable component but incorporation of genetic and genomic testing has not yet become widespread. In 2015 and 2016, two landmark papers led to a dramatic shift in understanding and now practice. Other articles in this issue will review therapeutic implications, genetic predisposition syndromes, multigene testing and polygenic risk scores. This brief article reviews germline genetic contributions to development of metastatic prostate cancer and how these genetic factors may inform management of prostate cancer early detection and early stage prostate cancer.

Early sequencing discoveries in prostate metastases involve DNA repair genes

Prior to 2015, understanding about molecular features of prostate cancer came largely from prostatectomies and biopsies. With the exception of a few select rapid autopsy programs, metastatic disease was understudied. Support from SU2C and PCF enabled an international, multi-institutional study to obtain metastatic biopsies and characterize mutational spectra. Results from the first 150 metastatic biopsies identified a high proportion of actionable mutations—including 23% with mutations in DNA repair genes such as BRCA2, ATM and BRCA1.1 Evidence was also mounting that prostate cancers with BRCA2 inactivation were highly susceptible to platinum chemotherapy,2,3 and the TOPARP-A study reported early compelling evidence that PARP inhibitors held similar promise.4 Notably, about half of the DNA repair mutations were germline, thus representing known or suspected autosomal dominant cancer predisposition syndromes.

Germline DNA repair gene mutations in metastatic prostate cancer patients

In 2016, a definitive study of 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, was conducted with targeted germline sequencing. Remarkably, 11.8% (82/692) had germline mutations in DNA repair genes—most frequently BRCA2, ATM, CHEK2 and BRCA1.5 Presence of germline mutation was not correlated with family history of prostate cancer or age at diagnosis. In the tumors available for sequencing, 67% (36/61) had evidence of second allele inactivation, evidence that germline alterations were biologically relevant rather than simply bystanders. These findings have been born out in other studies with largely similar, albeit population-specific, proportions.6,7

Address correspondence to Dr. Heather H. Cheng, Seattle Cancer Care, 825 Eastlake Avenue East, Seattle, WA 98109 USA
Individuality of DNA repair genes

DNA repair genes require further individual characterization. Key differences are already apparent in estimated cancer risk in germline carriers and as predictive biomarkers of treatment response. For example, germline mutations seen in metastatic disease are observed most commonly in BRCA2, which confers the highest prostate cancer risk, poor outcomes, and observed best responses to platinum and PARP inhibitors.

In comparison, germline BRCA1 mutations are also associated with elevated risk of prostate cancer, aggressive disease and response to DNA damaging agents, but less common and appears to confer attenuated risk of prostate cancer. Germline ATM pathogenic variants are more common in the general population yet are enriched in metastatic prostate cancer setting, this raises some uncertainty as to whether absence of function contributes to cancer initiation or to metastatic potential. Early data on response to PARP is in the setting of ATM inactivation suggests differences, not surprising due to different functions of BRCA2 and ATM proteins. Other genes are newly implicated with prostate cancer risk and still less characterized due to rarity, e.g. FANCA or RAD51C.

Collective registries and databases of rare variants in population-based and in metastatic settings will be essential. Table 1 summarizes current reported data, although additional data is emerging. For the sake of clinical trial enrollment, it is reasonable to take a more permissive approach in the metastatic setting,

### TABLE 1. Genes with potential clinical actionability

<table>
<thead>
<tr>
<th>Gene</th>
<th>Association with ↑ prostate cancer risk</th>
<th>Prevalence of germline mutations in metastatic prostate cancer</th>
<th>Prevalence of germline mutations in prostate cancer with fam hx</th>
<th>DNA damaging agents: PARP, platinum</th>
<th>Immune checkpoint inhibitors: PD-1 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>X</td>
<td>1.6%</td>
<td>2.0%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ATR</td>
<td>X</td>
<td>0.3%</td>
<td>Not evaluated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>X</td>
<td>0.9%</td>
<td>0.7%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>X</td>
<td>5.4%</td>
<td>4.7%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>0.2%</td>
<td>0.3%</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK12</td>
<td>(somatic only)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>X</td>
<td>1.9%</td>
<td>2.9%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>FAM175A</td>
<td>0.2%</td>
<td>Not evaluated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FANCA</td>
<td>-</td>
<td>Not evaluated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOXB13</td>
<td>X</td>
<td>Not evaluated</td>
<td>1.1%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>X</td>
<td>-</td>
<td>0.06%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>0.14%</td>
<td>Not evaluated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>X</td>
<td>0.14%</td>
<td>0.69%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>X</td>
<td>0.14%</td>
<td>0.45%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>*</td>
<td>0.3%</td>
<td>0.32%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>*</td>
<td>0.4%</td>
<td>0.56%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>X</td>
<td>0.3%</td>
<td>0.54%</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>0.14%</td>
<td>0.21%</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>0.4%</td>
<td>0.15%</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*emerging/limited data
*adapted from Cheng, et al 2019 JNCCN

© The Canadian Journal of Urology™: International Supplement, October 2019
especially if standard treatment options have been exhausted, and patients should be encouraged to participate in clinical trials and/or variant/mutation registries whenever possible.

Lack of diversity in data sets perpetuates health disparities

A notable health disparity in the USA is the fact that African American (AA) men are at higher risk for prostate cancer while also experiencing worse cancer outcomes. Causes are multifactorial, but likely include genetic factors. Since AA men and other racial/ethnic subgroups are underrepresented in genetic studies to date, there are fewer examples of affected and unaffected individuals contributing to higher rates of variants of uncertain significance (VUS). A recent report found similar rates of pathogenic variants in known cancer risk genes among AA men with prostate cancer, and prioritization of diverse representation in research efforts will help address gaps in knowledge and practice.

Incorporating emerging data into earlier disease state management and clinical research

The opportunities for more complete understanding of rare gene variants and VUS in underrepresented populations poses challenges, albeit surmountable, around best clinical practices. For localized disease management and/or early cancer detection approaches in germline carriers, clinical trials and variant registries should be encouraged whenever possible. There may be an increasing role for specialized cancer genetics clinics and tumor boards to synthesize available data (family history and somatic sequencing) and promote clinical and research advances.

Disclosures

HHC receives research funding from the Institute for Prostate Cancer Research, the Pacific Northwest Prostate Cancer SPORE CA097186, Prostate Cancer Foundation, NIH/NCI P30 CA015704, Clovis Oncology, Janssen, Medivation and Sanofi.

References

The AR-DNA repair axis: insights into prostate cancer aggressiveness

Karen E. Knudsen, PhD, MBA
Thomas Jefferson University, Sidney Kimmel Cancer Center, Philadelphia, Pennsylvania, USA


Despite significant advances in understanding the biology of advanced prostate cancer and approval of novel therapeutic agents, there is no durable cure for metastatic disease. Recent findings unmasked the importance of androgen receptor (AR) signaling in regulation of DNA repair, and alterations of the AR-DNA repair factor axis were shown to promote aggressive phenotypes including metastasis. These and related findings underscore the importance of determining impact AR-DNA repair factor alterations on prostate cancer progression.

Key Words: CRPC, androgen, DNA repair, DNA-PK, prostate cancer

Introduction

Prostate cancer remains the 2nd leading cause of cancer death in US men. Local prostatic adenocarcinoma can be effectively treated through radical prostatectomy or radiation therapy; however, non-organ-confined prostate cancer represents a major clinical challenge. First line treatment for non-organ confined disease consists of androgen deprivation therapy (ADT), as prostate cancer cells are exquisitely dependent on androgen receptor (AR) signaling for growth, survival, and as was recently shown, effective DNA repair. Notably, AR is a ligand-dependent transcription factor whose activity can be suppressed through pharmacological manipulation. ADT is elicited via GnRH agonists that suppress testicular androgen synthesis, (thus depleting AR of ligand), often complemented by use of direct AR antagonists. ADT is initially effective in the majority of patients, and successful suppression of AR activity is validated by loss of detectable prostate-specific antigen (PSA) in patient sera; PSA is encoded by a well-defined AR target gene, and serves as a biochemical readout of prostate-specific AR function. ADT results in a mixed population of tumor cell quiescence and cell death, resulting in remission. Unfortunately, this is transient (~2-3 years), and recurrent, “castrate-resistant” prostate cancer (CRPC) emerges for which there is no durable cure. This transition is driven by inappropriate AR reactivation in the majority of CRPC despite the continuation of ADT, leading to patient morbidity. Thus, it is critical to identify mechanisms beyond AR targeting, acting in concert with standard of care to either prevent or effectively manage CRPC.

DNA repair alterations are frequent in advanced disease

Emerging data from multiple studies recently demonstrated that alterations in DNA damage repair (DDR) pathways are more common than previously thought in sporadic prostate cancer, and that DDR alterations likely afford new, more effective means of therapeutic intervention in a subset of advanced disease. In an initial study which characterized the genomic landscape of metastatic CRPC (mCRPC), alterations of DDR genes were identified alterations in ~23% of cases, suggesting that dysregulation in DDR genes represents a significant driver of prostate cancer
progression. While suggestive that these alterations may be pathogenic drivers of disease progression or aggressive features, this concept has not been formally assessed, which limits the understanding of the biological consequence of prevalent DNA repair alterations. The need to experimentally assess putative DNA repair driver alterations and generate models to discern tumor relevance is underscored by prediction analyses of reported DNA repair alterations in both primary prostatic adenocarcinoma and in mCRPC.

AR is a critical regulator of DNA repair in prostate cancer and CRPC

The importance of DNA repair regulation (and alterations thereof) was further heightened by discoveries which revealed the critical role of androgen/AR signaling in regulating DNA repair competency. Initial findings identified the androgen receptor (AR) as a requisite effector of double-strand DNA repair that alters the response to genotoxic insult in advanced prostate cancer.5,6 This AR function proved dependent on the ability of AR to regulate expression and activity of DNAPK, an enzyme that is key for the process of repairing double-strand DNA breaks through non-homologous end joining, and has a parallel role as a transcriptional modulator.5 The impact of AR in regulating DNA repair is dependent on AR-induced DNAPK expression and activity.5 Further investigation demonstrated that AR-induced DNAPK activation promotes transcriptional networks that promote cell migration and metastasis, thus linking the AR-DNA repair axis to tumor progression and acquisition of aggressive tumor phenotypes.3 Strikingly, DNAPK is the most deregulated kinase in metastatic CRPC, and is independently predictive of metastasis and overall survival in patients with high risk disease.5 These findings not only nominate DNAPK as a biomarker to predict which tumors will go on to develop metastases, but identify DNAPK as a therapeutic target to treat or prevent advanced disease. Based on these studies, a clinical trial study is ongoing which will assess the impact of a DNAPK inhibitor (CC-115) in combination with Enzalutamide. Preclinical investigation showed that targeting DNAPK enhances response to AR-directed therapies, using both in vivo xenografts and ex vivo culture of primary human tumors.7 Combined, these studies strongly suggest that leveraging the dual functions of DNAPK in promoting DNA repair and metastatic progression will improve outcomes for advanced disease. Additional AR-dependent DDR factors (e.g. Ku70) have also been identified, which likely contribute to the impact of androgens/AR in promoting DNA break repair.8 Given these substantial functions and the association of AR-DDR axis perturbations with aggressive disease, determining the impact DDR alterations (both somatic and germline) on AR-mediated DNA repair will be critical for assessing the contribution of these genetic alterations to prostate cancer development and progression.

Disclosures

Dr. Karen E. Knudsen received research support from Celgene, Sanofi, Novartis and CellCentric and on the advisory board for CellCentric, Sanofi, Celgenem Atrin, Janssen and Genentech.

References

Molecular insights into the germline for prostate cancer initiation, progression, and aggressiveness

Colin C. Pritchard, MD, PhD
Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA


Germline and tumor genetic testing of DNA repair genes in men with advanced prostate is increasingly recommended by U.S. and international guidelines as part of standard of care. Damaging mutations in homologous DNA repair pathways genes including BRCA2, BRCA1, PALB2, and ATM, and mismatch DNA repair genes including MSH2 and MSH6 have emerging clinical utility for risk assessment and treatment decision-making. This article summarizes a presentation at the 2019 Philadelphia Consensus Conference focused on the latest data at the intersection of germline and tumor genetic testing for prostate cancer patients.

Key Words: BRCA1, BRCA2, ATM, MSH2, MSI, genetic testing

Introduction

Multiple large studies in the past 3 years have revealed a higher-than-expected prevalence of autosomal dominant high and moderate penetrance germline DNA gene mutations in men with advanced prostate cancer.1-5 At the same time, there is increasing evidence that loss-of-function mutations in DNA repair genes are highly predictive of treatment responses. This work has led to the rapid adoption of both germline and somatic (tumor) panel testing for DNA repair genes in men with advanced prostate cancer. The emerging model for care of men with advanced prostate cancer involves genetic testing to guide therapy, risk assessment, and risk counseling.

Materials and methods

Literature review was performed of recent large prostate cancer studies into germline and somatic DNA repair gene mutation prevalence estimates, clinical utility for treatment, and tumor features that may help providers identify potential germline carriers. Review was mostly limited to DNA repair genes in the homologous recombination (HR) and mismatch repair (MMR) pathways in which there are well-known risk syndromes. The overall prevalence of germline pathogenic and likely pathogenic mutations in BRCA2, BRCA1, PALB2, ATM (HR) and MSH2, and MSH6 (MMR) among five large studies is summarized in Table 1. There are many additional genes that have been evaluated in prostate cancer in these pathways. Among HR and MMR genes BRCA2 is the most commonly mutated in the germline and among MMR, MSH2 is most common.

Features of prostate cancer patients harboring damaging germline mutations in key HR and MMR genes are listed in Table 2, including relative prostate cancer risk, expected family history and other cancer risks, tumor features that are characteristic in patients harboring mutations for each specific gene, and level of evidence of treatment responses. For most of the HR and MMR genes there are not yet well-characterized lifetime prostate cancer risk estimates. Risk of other cancers are well-defined for many of these genes and can provide clues from the family history.

Tumor features are associated with specific germline pathogenic variants but are not specific. For patients harboring germline HR DNA repair mutations, particularly in BRCA2, the presence of intraductal or ductal histology is often present.6-7 Newer assays are becoming available to assess a “BRCAness” mutational signature in prostate tumors but are not yet standard-
### TABLE 2. Features of DNA repair genes commonly tested in men with prostate cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathway</th>
<th>Prostate cancer risk</th>
<th>Other family history</th>
<th>Tumor features</th>
<th>PARP/platinum response</th>
<th>Anti PD1/PDL1 response</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>HR</td>
<td>High</td>
<td>Br, Ov, Panc</td>
<td>Intraductal/ductal</td>
<td>++++++</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>HR</td>
<td>Moderate</td>
<td>Br, Ov</td>
<td>Intraductal/ductal</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>HR</td>
<td>Mod/high</td>
<td>Br, Ov, Panc</td>
<td>Intraductal/ductal</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>HR</td>
<td>Moderate</td>
<td>Br, Ov</td>
<td>Intraductal/ductal</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>HR</td>
<td>Moderate</td>
<td>Br, Ov, CRC</td>
<td>Emerging</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>HR</td>
<td>Some data</td>
<td>Br</td>
<td>Emerging</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>HR</td>
<td>Emerging</td>
<td>Ov</td>
<td>Emerging</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>HR</td>
<td>Emerging</td>
<td>Ov</td>
<td>Emerging</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>HR</td>
<td>Emerging</td>
<td>Ov</td>
<td>Emerging</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>FANCA</td>
<td>HR</td>
<td>Unknown</td>
<td>?</td>
<td>Emerging</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>MMR</td>
<td>High</td>
<td>CRC, endo</td>
<td>MSI, Gl. 5, ductal, ↑TMB</td>
<td>++++++++</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>MMR</td>
<td>Moderate</td>
<td>CRC, endo</td>
<td>MSI, Gl. 5, ductal, ↑TMB</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>MMR</td>
<td>Moderate</td>
<td>CRC, endo</td>
<td>MSI, Gl. 5, ductal, ↑TMB</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>MMR</td>
<td>Some data</td>
<td>CRC, endo</td>
<td>MSI, Gl. 5, ductal, ↑TMB</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

HR = homologous recombination DNA repair; MMR = mismatch DNA repair; Br = breast cancer; Ov = ovarian cancer; Panc = pancreatic cancer; CRC = colorectal cancer; endo = endometrial cancer; intraductal/ductal refer to rare histologic subtypes; Gl = primary Gleason grade; MSI = microsatellite instability; TMB = total mutation burden

### TABLE 1. Germline mutation prevalence in selected DNA repair genes in advanced prostate cancer

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>692</td>
<td>313</td>
<td>319</td>
<td>1328</td>
<td>3,607</td>
<td>6259</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5.3%</td>
<td>3.5%</td>
<td>5.0%</td>
<td>4.5%</td>
<td>4.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>0.9%</td>
<td>0.6%</td>
<td>0.3%</td>
<td>1.1%</td>
<td>1.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.4%</td>
<td>NA</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>ATM</td>
<td>1.6%</td>
<td>1.9%</td>
<td>0.3%</td>
<td>1.8%</td>
<td>2.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>MSH2</td>
<td>0.1%</td>
<td>NA</td>
<td>0.0%</td>
<td>0.5%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>MSH6</td>
<td>0.1%</td>
<td>NA</td>
<td>0.0%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

*these studies included some patients with localized disease

of care. These assays will assist in the future in helping to determine whether a germline pathogenic mutation in an HR gene is a driver of the cancer. Particularly for moderate to low penetrance genes such as ATM or CHEK2 one cannot assume that a prostate cancer is driven by an underlying germline pathogenic mutation.

For prostate cancer patients harboring germline MMR DNA repair mutations (Lynch syndrome patients), tumors will often have microsatellite instability (MSI). MSI is the genomic hallmark of MMR deficiency (MMRd) and a reliable way to determine if the underlying germline MMR mutation was part of tumorigeneses. However, many MSI assays have not been well-validated for prostate cancer so the sensitivity is not optimal. Another tumor clue to MMRd is elevated total mutation burden (TMB), a test increasingly performed as part of a next-generation sequencing large panel tumor assessment. Histologic clues that point to
Molecular insights into the germline for prostate cancer initiation, progression, and aggressiveness

Lynch syndrome include very high histologic grade (primary Gleason pattern 5) and ductal histology. In prostate cancer patients with primary Gleason pattern 5 about 8% had either germline or somatic mutations in MSH2, and in patients with ductal histology about 20% had a germline or somatic mutation in a key MMR gene.

There is now good evidence that advanced prostate cancer patients harboring BRCA2 and BRCA1 HR DNA repair mutations response to treatments with poly (ADP) ribose polymerase (PARP) inhibitors as well as platinum-based chemotherapy. Evidence for PARPi/platinum responses is emerging for other HR DNA repair genes, Table 2. Similarly, there is strong evidence that MMRd results in favorable response to checkpoint blockade immunotherapy, with pembrolizumab being approved for all tumors (including prostate cancer) with evidence of MMRd. It is worth restating that prostate cancer patients with Lynch syndrome may not have MMRd in their tumors. This is particularly true for patients with germline PMS2 or MLH1 mutations.

In summary, the past few years have been exciting time for genetic testing in prostate cancer as evidence is emerging quickly for clinical utility in risk assessment and treatment decisions.

Disclosures

Dr. Colin C. Pritchard is a consultant for Promega.

References

African American and Asian males: what do we know about germline predisposition to prostate cancer

Curtis A. Pettaway, MD
Department of Urology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA


There is a paucity of data related to highly penetrant genes associated with a genetic predisposition to prostate cancer or its virulence among men of diverse ancestral populations including African American and Asian men.

Key Words: African American, Asian, prostate cancer, germline DNA testing

Introduction

African American (AA), Asian, and Caucasian males exhibit both a disparate incidence and mortality from prostate cancer with AA men having a higher incidence and mortality and Asian males a lower incidence and mortality from prostate cancer when compared to Caucasians. Genetic predisposition to prostate cancer is now widely recognized given the discovery of highly penetrant gene mutations associated with several hereditary cancer syndromes (HCS) such as BRCA1/2 (Hereditary Breast and Ovarian Cancer [HBOC], HOXB13 mutations associated with Hereditary Prostate Cancer [HPC] and most recently the mismatch repair gene mutations MLH1, MSH2 associated with Lynch syndrome [LS]). Among these HCS prostate cancer incidence is increased. Further BRCA1/2 and other DNA repair gene abnormalities (ATM, CHEK2) have been detected among patients with lethal and metastatic prostate cancer and can influence subsequent response to therapy. Recently germline-testing recommendations have been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for the management of prostate cancer.

Materials and methods

We performed a PubMed search for articles under the subjects of AA, Asian, and the following terms including: hereditary prostate cancer, BRCA1/2, DNA repair genes, and Lynch syndrome from 1995 to the present. Manuscripts that included African or Asian American prostate cancer patients that underwent germline DNA testing and included information related to the incidence and types of mutations found in addition to any associated prostate cancer phenotypic information among affected individuals were included.

In two studies including 293 AA prostate cancer patients tested the incidence of BRCA1/2 mutations was 0%-4%. In a single recent study with 73 unselected Asian prostate cancer patients tested, BRCA1/2 mutations were found in 5 (7%) patients. Among the two AA cohorts with 293 prostate cancer patients HOXB13 mutations were noted in 5 (7%) patients with no mutations found among 73 Asian subjects. DNA mismatch repair gene abnormalities (MSH2, MLH1, MSH6, PMS2) were noted in only one of 227 (0.4%) AA patients and two of 73 (2.7%) Asian patients.
African American and Asian males: what do we know about germline predisposition to prostate cancer

In a recent multi racial/multiethnic study where 3706 prostate cancer subjects underwent germline multi-gene testing irrespective of family history, cancer stage and grade the cohort consisted of 2594 white men, 234 men identified as Ashkenazi Jewish, 227 Black/AA, 78 Hispanic, 73 Asian, and 401 men categorized as “other” (i.e., not belonging to any of the former groups). Only mutations classified as pathogenic, likely pathogenic, or increased disease risk were classified as positive. Mutations of unknown significance were recorded but not classified as positive. Among the cohort the overall incidence of genetic alterations was 620 (17.2%) with BRCA1/2 mutations in 30.7%, HOXB13 in 4.5% and DNA mismatch repair alterations in 1.74% of the cohort. Of note the incidence of alterations was not affected by subject age or tumor grade. Family history among this prostate cancer cohort of breast, ovarian, colon, or pancreatic cancer also did not correlate with the incidence of abnormalities. Of note Hispanic and Black patients had a lower incidence of genetic alterations (6.8%-10% respectively) when compared with the white and Ashkenazi Jewish cohorts (17%-22%). Overall DNA repair gene alterations were less common among non-white/non Jewish cohorts. Among the unselected AA cohort the most frequent mutated genes were BRCA2 (2.6%), BRCA1 and HOXB13, ATM (1.3% each) and ATM, PALB2, MUTYH, CHECK2, CFTR, PMS2, RAD51C, SMAD4 (all at 1 each [0.8%]).

The Asian population exhibited the following mutations including BRCA2 (4.1%), BRCA1 and ATM (at 2.7%), with MSH6, PALB2, PMS2 and RET at 1.3% each.

Another recent study characterizing DNA repair gene alterations among a cohort of men with lethal versus localized prostate cancer found BRCA2 and ATM mutation carriers died at a younger age, and exhibited a decreased time to death when compared to non carriers. Among this cohort with lethal prostate cancer mutations in either BRCA2 or ATM were noted in 5.36% of European Americans, 3.33% of African Americans, and 18.1% of Chinese patients versus in 0%-1% of men with localized cancer. In the study by Prichard et al specifically characterizing DNA-repair gene mutations among a multiethnic cohort that included Caucasians (n = 912) as well as small numbers of black (n = 98), Hispanic (n = 15) and Asian (n = 24) men the incidence of mutations increased when comparing localized to metastatic patients among each cohort (Caucasian = 4.4 versus 12.1% respectively, Black = 6.8 versus 10% respectively, Hispanic = 14 versus 37.5% respectively, Asian = 0 versus 8.3% respectively.

When evaluating probands with cancers likely related to HCS and a family history of prostate cancer Chandrasekar et al recently found a disparate pattern of germline DNA mutations.

Among AA probands (n = 53) with a HCS and family history linked to prostate cancer germline mutations among the AA cohort involved solely BRCA1/2 whereas among the Caucasian cohort (n = 292) germline mutations were noted in a spectrum genes.

Conclusion

Accumulating data suggest that men of African and Asian ancestry with prostate cancer and their families may exhibit genetic abnormalities in highly penetrant genes associated with prostate cancer and virulent disease. Given the small cohort sizes of the populations reported thus far, prospective studies with large cohorts of men of diverse ancestry, detailed family history across a spectrum of prostate cancer disease states, with multigene testing panels is needed to define more precisely the optimal patients who should be tested. In addition such data will enable rationale tailoring of gene panels to optimize patient management as well as family counseling.

Disclosure

Dr. Curtis A. Pettaway received research funding from Beckmann Coulter and MDx Health.

References

Prostate cancer genetic testing: NCCN familial high-risk assessment: breast/ovarian
Mary B. Daly, MD, PhD
Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines have become the most recognized standard for clinical policy in cancer care. The Genetic Breast and Ovarian Guideline was introduced in 1999 with an emphasis on BRCA1/2. Based on evidence linking prostate cancer to the BRCA genes, prostate cancer was added to the guideline as a criterion for risk assessment in 2013. The current criteria include aggressive/metastatic disease and family history of BRCA-related cancers.

Key Words: prostate cancer, BRCA genes, genetic testing, risk management

The genetic/familial risk assessment

Breast and Ovarian Guideline was first introduced in 1999 with an emphasis on the BRCA1/2 genes. Over the years the scope has broadened to include other genes and other cancers shown to be related to hereditary breast/ovarian syndrome. Based on evidence linking both aggressive prostate cancer and a family history of BRCA-related cancers to the BRCA genes, it was first added to the guideline as a criterion for risk assessment in 2013. NCCN relies on the growing body of evidence which is helping to further characterize the features of prostate cancer which indicate a heritable component. While earlier studies failed to find an association between the three founder mutations in the Ashkenazi population with prostate cancer, a large case-control study found a significantly increased risk of prostate cancer in carriers of the BRCA2 founder mutation, but not in carriers of the two BRCA1 founder mutations. A subsequent case-control study found both an increased risk of prostate cancer in Ashkenazi prostate cancer
patients who carried a BRCA2 mutation, and a higher risk of poorly differentiated histology, recurrence and prostate cancer-specific death.\textsuperscript{3} A retrospective analysis of clinical outcomes of non-AJ prostate patients with germline BRCA mutations in the UK found that poorly differentiated cancer, advanced stage, nodal involvement and metastatic disease were all more common in carriers than non-carriers. In this population, median overall survival was significantly decreased in BRCA2 carriers compared to non-carriers.\textsuperscript{4}

A multicenter study evaluated the frequency of mutations in a series of 20 DNA-repair genes, including the BRCA genes, in men unsel ected for family history who had metastatic prostate cancer. At least one presumed pathogenic germline mutation involved in DNA-repair was found in 11.8\% of men. Of these, 44\% of mutations were in the BRCA2 gene. The odds ratio of finding a DNA-repair gene among men with metastatic prostate cancer was 5.3 compared to a control group of men with localized low-to-intermediate-risk tumors. Metastatic disease in this study was a better predictor of a DNA-repair mutation than was a family history of prostate cancer.\textsuperscript{5} Mutation status of BRCA1/2 and ATM was a significant predictor of lethal disease in a case-case study which compared men who died from prostate cancer to those with low-risk localized disease. The association of lethality and mutation status was observed in Caucasian, African American and Chinese men.\textsuperscript{6} A predominant finding in all of these studies is the much greater association of BRCA2 with prostate cancer compared to BRCA1. The current guideline includes prostate cancer with a Gleason score of \( \geq 7 \) in the context of a family history of other BRCA-related cancers, or metastatic prostate cancer as indications for genetic testing. The current guideline also recognizes the potential benefit of testing of men with prostate cancer for targeted therapeutic options.

There is less evidence to guide screening recommendations for men with hereditary prostate cancer. The IMPACT screening network is following a cohort of men with BRCA1/2 mutations and a control group of true negative BRCA1/2 men to determine the optimal screening protocol for men with germline BRCA mutations. Using a PSA threshold of 3.0 ng/mL for considering prostate biopsy, their first screening round found a positive predictive value of 48\% among BRCA2 carriers, which is double that seen in population screening studies.\textsuperscript{7} This cohort will continue to be followed to provide further data on the value of regular screening in BRCA men. The current NCCN guideline recommends prostate cancer screening for BRCA2 carriers, and a consideration of prostate cancer screening for BRCA1 carriers. It directs readers to the Guidelines for Prostate Cancer Early Detection.

Cancer genetics is a constantly evolving field and NCCN will continue to update its guidelines as more evidence becomes available. Some of the pressing questions are: what other genes are associated with prostate cancer, and what is their prevalence and penetrance? What additional therapeutic options may become available based on mutation carrier status; what is the optimal threshold for PSA level in screening mutation carriers; and what is the role of MRI scanning in detecting early stage prostate cancer.

Disclosures

Dr Mary B. Daly has no disclosures.

References

Germline testing in those at risk of prostate cancer

Peter R. Carroll, MD, MPH, John S. Witte, PhD, J. Kellogg Parsons, MD, MHS

Department of Urology and UCSF - Helen Diller Comprehensive Cancer Center, University of California, San Francisco and the Department of Urology, University of California, San Diego, California, USA


Men with germline mutations in DNA repair genes are at an increased risk of prostate cancer. These germline mutations are commonly seen in conjunction with somatic DNA repair gene mutations in prostate tumors. This indicates that men with a personal or family history of prostate cancer—as well as other cancer syndromes arising from mutations in DNA repair genes—should be considered for genetic testing and counseling.

Key Words: prostate cancer, genetic testing, germline mutations

Recent data indicate that men with germline mutations in DNA repair genes are at an increased risk of prostate cancer. These germline mutations are commonly seen in conjunction with somatic DNA repair gene mutations in prostate tumors.1,2 This indicates that men with a personal or family history of prostate cancer—as well as other cancer syndromes arising from mutations in DNA repair genes—should be considered for genetic testing and counseling.3

Germline mutations in a number of homologous DNA repair genes have been observed in men with prostate cancer, including (in approximate order of frequency observed in cases): BRCA2, ATM, CHEK2, BRCA1, MUTYH, RAD51D, PALB2, ATR, NBN, PMS2, GEN1, MSH2, MSH6, RAD51C, MRE11A, BRIP1, or FAM175A.4,5 Moreover, germline mutations in DNA repair genes occur at a higher rate in men with metastatic prostate cancer than in men with localized disease.5 This finding is clinically noteworthy in that men with metastatic prostate cancer and DNA repair mutations respond well to poly-ADP ribose polymerase (PARP) inhibitors and platinum-based chemotherapy.6,7

A recent study of 3607 men with prostate cancer who were clinically referred for genetic testing found that 17% carried a tested germline mutation, with 11.5% in BRCA2, CHEK2, ATM, BRCA1, or PALB2.4 However, in this population, Gleason scores and family history were not associated with variant detection, and a relatively large percentage of men carrying genetic mutations (> 30%) would not have been screened using the current NCCN guidelines.4

Germline BRCA1 and BRCA2 mutations (associated with hereditary breast and/or ovarian cancer syndrome) occur in approximately 0.2% to 0.3% of the
Germline testing in those at risk of prostate cancer

general population, with higher rates seen in certain racial/ethnic groups. These mutations have been associated with an increased risk for prostate cancer in numerous reports. In particular, BRCA2 mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association of BRCA1 mutations and increased risks for prostate cancer are less consistent. Furthermore, prostate cancer in men with germline BRCA mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in non-carrier patients. Among lethal prostate cancer cases, 60% of mutation carriers of BRCA1/2 and ATM report a negative family history.

Results from the first round of screening of the IMPACT study, which enrolled men aged 40 to 69 years with germline BRCA1/2 mutations and a control group of men with wild-type BRCA1/2 who are related to mutation carriers, were recently reported. Whereas it was evident that there was no difference between carriers and controls in the rate of prostate cancer detection or the PPV of biopsy for detecting cancer in men with PSA > 3.0 ng/mL, a significant difference was seen in the PPV of biopsy for detecting intermediate/high-grade cancer in BRCA2 carriers with PSA > 3.0 ng/mL (2.4% versus 0.7%; p = .04). Future rounds of screening in this trial may help inform the best strategy for screening in this high-risk population.

Men with Lynch syndrome (germline mutations in DNA mismatch repair genes MLH1, MSH2, MSH6, PMS2, or EPCAM) have a 2- to 5.8-fold increase in risk for prostate cancer. Age of onset and aggressiveness of prostate cancer in these individuals, however, do not generally appear to be different than in sporadic cases. Carriers of the G84E mutation of the HOXB13 gene also have a significantly higher risk for prostate cancer and are more likely to have early-onset familial disease. HOXB13 mutations are more frequent among families of Scandinavian heritage.

There is a significantly increased risk of a family history of first-degree relatives with non-prostate cancers among men with mutations in DNA repair genes. This is especially meaningful for three reasons: 1) men with DNA repair mutations have been shown to be candidates for specific therapeutics; 2) the detection of mutations in DNA repair genes can inform personalized screening strategies; and 3) because the mutations are germline and implicated in various malignancies, they help to identify whole families that may be particularly susceptible to cancer.

Commercial panels are now available to assess most of the main high-penetration prostate cancer risk genes. Information regarding the status of high-risk germline mutations should be used as part of the discussion about prostate cancer screening; patients may not be aware of the increased risk for prostate cancer associated with such mutations.

Disclosures

Dr. Peter R. Carroll and Dr. John S. Witte have no disclosures.
Dr. J. Kellogg Parsons is an investigator for Dendreon.

References


Current recommendations for prostate cancer genetic testing: NCCN prostate guideline

James L. Mohler, MD,1 Celestia S. Higano, MD,2 Edward M. Schaeffer, MD, PhD,3 Heather H. Cheng MD, PhD2

1Departments of Urology and Pharmacology and Therapeutics, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA
2Division of Medical Oncology, University of Washington, and Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
3Department of Urology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois, USA

DNA sequencing has become less expensive and patients are requesting sequence information more often. The clinical utility of identifying genomic and/or somatic mutations remains uncertain in most cancers and especially in prostate cancer. However, clinical guidelines must offer guidance. The rapidly expanding knowledge base requires that guideline panels pay vigilant attention to the literature, advocate for clinical trials and correlative science, and provide frequent guideline updates.

Key Words: prostate cancer, genomic and somatic sequencing, genetic counseling

Process used to develop the genetic testing sections of the NCCN guidelines for prostate cancer

The rapid evolution of knowledge about genomic and somatic mutations in prostate cancer necessitated that the Prostate Panel procure additional expertise to improve the 2019 guideline. Additions to the algorithms and principles caused a posting delay until March 2019 (normally posted in November; the 2019 guideline is in version 4 already.1 The changes made were explained in greater detail in a manuscript first authored by our expert2 and in the manuscript section of the guideline. Presentations of new data at the panel in-person meeting June 27, 2019 will improve the 2020 guideline.

Key features of the genetic testing sections of the NCCN guidelines for prostate cancer

In clinically localized prostate cancer, PROS-1 describes the elements of a proper family history for known germline variants (footnote c) and the family history...
criteria to prompt germline testing (footnote d). Only high or very high-risk groups warrant consideration of germline testing in the absence of a positive family history (footnote k). PROS-9 recommends germline testing for all men who present with regional or metastatic prostate cancer (footnote k) and consideration of somatic testing to uncover germline mutations (footnote l) and to uncover mutations that may impact future therapy (footnotes dd and ee).

Figure 1. Criteria for germline genetic testing.

Figure 2. Tumor and somatic testing.

Genetic testing algorithms for use in the clinic

An extensive family history of cancer, Figure 1, should prompt recommendation for germline testing. While family history is a necessary component of history gathering, it is not sufficient for identifying many men carrying germline genetic variants/mutations associated with cancer risk. Regional or metastatic prostate cancer\(^3^,^4\) and intraductal\(^5\) or ductal\(^5^,^6\) histology has a higher association with germline cancer risk mutations.

Somatic (tumor) testing has greatest relevance in the metastatic setting, but may be important in the regional setting, Figure 2. Clinical trials are testing targeted therapies in earlier disease states (www.clinicaltrials.gov). Pembrolizumab is a treatment option for advanced prostate cancer with evidence of microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) and after failure of prior approved agents in the metastatic (m) castration-resistant prostate cancer (CRPC) setting. Earlier use of platinum-based chemotherapy\(^7^,^8\) or enrollment on clinical trials testing PARP inhibitors\(^9\) (phase II and
III studies are in process that include the phase III PROFOUND study of olaparib in mCRPC) may be warranted in prostate cancer patients with homologous recombination DNA repair alterations.

Tumor/somatic testing may reveal a gene mutation that is potentially germline. Identifying somatic mutations in genes associated with cancer predisposition may suggest need for reflex genetic counseling for confirmatory germline testing, if not already done.

Understanding the potential outcomes of germline testing and responsibilities of the ordering provider for follow up is critical since workflows vary across practices, Figure 3. For example, if a germline pathogenic variant or likely pathogenic variant (i.e. mutation) is identified in a gene associated with cancer risk, follow up genetic counseling, if not already done, is essential to ensure appropriate patient understanding and appropriate cascade family testing (testing of at-risk relatives). In addition, patients with very strong family histories of cancer (high pre-test suspicion) and/or who are found to carry variants of uncertain significance (VUS) may have opportunities for research studies, in which new genes or variants are identified, or VUS may be reclassified.

Integration of genetic testing in to clinical practice

Most practices have focused on better history taking and, in cases of increased risk of genomic mutations, proceeding with (i) genetic testing and, if positive, referral for genetic counseling, (ii) genetic counseling educational videos with possible testing or (iii) genetic counseling followed by possible testing. Somatic mutations may be sought in metastatic prostate cancer, especially CRPC, and especially when considering change in therapy, Figure 4.

Genomic testing may use targeted (about $250 self-pay to $2500 for full BRCA analysis) or next generation sequencing (NGS; about $3500) but NGS tests are neither designed nor validated for germline assessment. The utility of germline variant identification remains uncertain. For example, identifying a BRCA1 or BRCA2 mutation is not sufficient, since many lack known function.10

Genetic counselors are highly trained medical professionals with expertise in counseling, addressing questions and anxiety about testing, and facilitating intra-family communication and appropriate follow up. They play essential roles in the processes described...
above, but are in high demand and limited supply, so that close partnership to optimize and triage their resources is necessary and will require more providers to become familiar with basic information about genetics and to take on certain aspects of pre-test counseling.

The Prostate Panel continues to deal with the explosion of genetic information, interacts with the Prostate Cancer Early Detection Panel, and hopes to provide congruency with the Breast, Ovarian and Colorectal guideline genetic recommendations. Best practice recommendations will emerge with more data and experience.

Disclosures

The authors have no disclosures.

References

Current prostate cancer genetic testing capabilities and considerations

Robert Pilarski, MS, LGC, MSW
Division of Human Genetics, James Comprehensive Cancer Center, Columbus, Ohio, USA


With the advent of next-generation sequencing technologies, genetic testing of prostate cancer patients is now typically done using multi-gene panels. These vary from targeted disease-specific panels to comprehensive (pan-cancer) panels, with advantages and disadvantages for each. This paper reviews a number of issues raised in choosing the best panels and labs to use, and issues presented by the increasing availability of direct-to-consumer testing.

Key Words: prostate cancer, genetic testing, gene panels, direct to consumer

Introduction

With the introduction of next-generation sequencing, clinical practice has rapidly moved from testing individual candidate gene(s) to the simultaneous testing of multiple genes on a single panel.1 While this has decreased costs and accelerated identification of patients with mutations, panel testing raises its own concerns.

Disease-specific versus broader panels

Some panels are disease-specific, testing only for genes known (and/or suspected) to be associated with a given condition such as prostate cancer. The advantages of this are that it reduces the likelihood of getting a result in a gene that either does not explain the patient’s history, or that raises unexpected management issues (e.g., prophylactic surgery) for cancers that weren’t previously of concern to the family. The disadvantages are that it may fail to test for syndromes that don’t clearly entail prostate cancer risk but do present significant risks for other cancers.

It may also fail to identify families with an atypical presentation of a syndrome. For example, Lynch syndrome is classically associated with GI, uterine, ovarian cancers. Recently, however, some evidence has suggested an association with a moderate-risk for prostate cancer as well.2 Ordering a prostate-specific panel that does not include the Lynch syndrome genes could fail to identify an affected family. Thus using broader panels increases the chance of identifying a hereditary syndrome. However this comes at the risk of an increased likelihood of identifying a variant of uncertain significance, as well as an increased chance of finding a mutation in a gene that does not explain the prostate cancer and/or is not clinically actionable.

Clinically-actionable panels

As a compromise, many labs offer “clinically-actionable” panels whose genes all have established management guidelines (for at least some cancer types) if a mutation is found. These panels may often include genes for cancers other than prostate cancer, however. In addition, the “actionability” of most genes is not clearly established for prostate cancer management, and the benefits may be more for managing the risks of cancers other than of the prostate. A purely clinically-actionable panel might also leave out probable prostate cancer genes without established management guidelines, such as HOXB13.

Address correspondence to Robert Pilarski, MS, LGC, MSW, Division of Human Genetics, Department of Internal Medicine, The Ohio State University, 2012 Kenny Road, Columbus, OH 43221 USA
Available prostate-specific panels

Currently at least six major testing labs offer prostate-specific gene panels (Ambry Genetics, Baylor, Fulgent, GeneDx, Invitae and Prevention Genetics). Of these, all six labs include the BRCA1 & 2, CHEK2, NBN and TP53 genes, and five also include ATM, the Lynch syndrome genes and HOXB13. Four of these labs also offer PALB2 and RAD51D, and three labs include BRIP1 and RAD51C. One lab offers ATR, FANCA and GEN1 as well. Thus a variety of panel options are available even within a small number of labs.

Selecting a laboratory

While there are a number of well-established laboratories in the cancer-genetics field, there are also an increasing number of start-up labs offering services that may appear to match those of established companies. When picking a laboratory, a number of questions should be asked. Among others, these include:
1. Are the lab directors experienced and appropriately trained?
2. Is the lab accredited?
3. What tests does the lab perform (limited or broad spectrum)?
4. Are the appropriate genes included on the panels offered?
5. What testing methodologies are used? What is the depth of coverage (average versus minimum) for their panels? Is Sanger sequencing used to confirm positive results?
6. How robust is their program for classification of variants of uncertain significance? Are providers re-contacted if a variant is reclassified?
7. What are the list prices versus costs to patients?
8. What are the billing and patient financial assistance policies of the lab?

Direct-to-consumer (DTC) testing

To complicate matters, a number of companies now offer DTC testing that includes prostate cancer risks. Although some of these companies offer next-generating sequencing similar to traditional testing, most are offering SNP-based panels that can only indicate a genetic association with prostate cancer risk, rather than identification of an actual causative gene mutation. In addition, most of these do not provide pre- or post-test genetic counseling, so that patients who present to a provider with these results often have little or no understanding of what they mean. Some labs doing association-type studies will provide their raw data to a patient, who can then go to a third party provider to have this data analyzed. Positive results received from this type of testing should always be confirmed in a traditional clinical lab since the rate of false positives is high. Not surprisingly, additional time, effort and expense are required to clarify these situations with patients.

Summary

In summary, providers are faced with an increasingly complex array of genetic testing choices that require careful consideration and navigation. As always, patients need to be fully informed before consenting to prostate cancer genetic testing and at receipt of results.

Disclosures

Dr Robert T. Pilarski has no disclosures.

References

Genetic counseling considerations for men with prostate cancer

Ashley H. Woodson, MS, CGC
Department of Clinical Cancer Genetics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA


Genetic counseling for men with prostate cancer has unique considerations. While the main components of the genetic counseling session are similar to other indications, specific attention to penetrance differences among hereditary cancer genes for male versus female-related cancer risks and future cancer surveillance among prostate cancer patients should be included. Limitations in discerning the contribution to prostate cancer and risks to relatives dependent on specific gene mutations, or absence of identifiable genetic cause, must be reviewed.

Key Words: genetic counseling, genetic testing, prostate cancer

Introduction

Improved knowledge of single-gene hereditary causes for prostate cancer has made genetic counseling (GC) and genetic testing (GT) increasingly prevalent. The major components of a GC session include contracting, collecting personal and family cancer histories, describing hereditary cancer syndromes, conveying genetic risk assessment (GRA), reviewing screening and prevention strategies, and discussing GT options, all to promote informed decision making.\(^1\) Expanding access to GC/GT services requires attention to the necessary components, particularly when developing new GC service delivery models. Recently, a survey of men pursuing multigene testing for inherited prostate cancer through alternative delivery models indicated men receiving GC via pre-test video and post-test phone disclosures were more likely to misunderstand results.\(^2\) Therefore, reviewing considerations in hereditary prostate cancer GC may guide efficacy of future models.

Contracting

Initial discussion with an individual presenting for GC involves a mutually agreed upon agenda and goals. In the era of precision medicine, a specific discussion may need to address the differences of somatic and germline GT. Many patients with advanced stage prostate cancer undergo tumor genomic profiling for targeted therapies and may have confusion between tumor specific analysis and germline GT. Defining these forms of GT is beneficial to ensure understanding.

Collecting personal and family cancer histories

Advanced stage prostate cancer is an indication for GT. Verifying the individual’s diagnosis, Gleason Score, cancer stage, and treatment plans guides the appointment to the most relevant information for the patient, including likelihood of a positive result, future screening recommendations, and impact on care. Studies show accuracy of cancer histories in first degree relatives is relatively high but significantly decreases with each further degree of relation.\(^3\) Limitations in family history knowledge, including
confusion between primary site and metastases, female gynecologic cancers, and benign neoplasms versus invasive cancer, may lead to GRA inaccuracies. Relevance in a prostate cancer population should be noted given the proband may be older at the time of assessment due to the later average age of prostate cancer diagnosis and lack knowledge of health histories for extended relatives.

Hereditary cancer risk assessment

Prostate cancer is highly heritable with many men having positive family history. The GRA is complicated by the limitations in discerning families with germline variants and those with a combination of polygenic and environmental factors. Explaining differences in these underlying causes of prostate cancer to individuals with a familial prostate cancer pattern is important. While multigene testing for rare hereditary prostate cancer genes explains some family histories, a negative genetic test result may not address the elevated risks of prostate cancer for male relatives.

Cancer syndrome information

Reviewing hereditary breast and ovarian cancer (HBOC) is critical when testing individuals with prostate cancer. Men focused on potential cancer risks for themselves and close male relatives should also be aware of higher breast and ovarian cancer rates among women with HBOC. Conversely, explaining limited evidence of prostate cancer risk associated with moderately penetrant genes, CHEK2 and ATM, helps convey the impact of test results. If multigene panel testing is considered, an explanation of hereditary cancer syndrome diagnoses outside the phenotype present in the personal and family history is warranted.

Early detection and prevention strategies

Identifying families with hereditary cancer syndromes aims to improve detection of future cancers, both in the individual and family members. Special consideration of disease stage should be given when discussing future cancer risks for early stage patients versus potential interventions and treatment options for those with metastatic prostate cancer. Pre-test GC session should include discussion of predictive familial testing if a germline mutation is identified. Dissemination of this information may occur by direct conversation by the proband with relatives, family letters, social media, or research studies focusing on family outreach efforts.

Genetic testing options

Multigene testing offers analysis of genes associated with prostate cancer but may also examine cancer syndromes beyond that of hereditary prostate cancer. Initial GC evaluation must explain the potential range of outcomes. Additionally, not all insurance providers cover GT. Consideration of an individual’s insurance provider, potential out of pocket costs, research study programs covering GT cost is necessary for test selection. While uptake of GT is reportedly high in this population, an opportunity to decline GT is a critical point of informed consent. Not all individuals will opt to pursue GT for various reasons.

Conclusion

GC for men with prostate cancer has unique considerations. The older age of the male prostate cancer population will alter particular stage of life concerns and potential impact a positive result will have on both the individual and their family members, such as adult-aged children, who may have independent thoughts on GT. Given most men assessed for hereditary prostate cancer are advanced stage, special consideration should be given to potential therapeutic options and impact on family members. Swiftly evolving guidelines of hereditary prostate cancer reinforces the need to optimize GC and recognize the unique elements in this population.

Disclosures

Ashley H. Woodson has no disclosures.

References

Alternate delivery models for genetic counseling: clinical and implementation considerations

Alanna Kulchak Rahm, PhD
Geisinger Genomic Medicine Institute, Danville, Pennsylvania, USA

Introduction

The incorporation of genomic information for cancer care has experienced exponential growth in recent years, and with this growth has come the ever-increasing demand for genetic counseling services and alternate service delivery models. Many of these models have varying levels of evidence compared to traditional in-person genetic counseling and have rarely been evaluated for multi-level impact at the patient, provider, and system levels. As important as generating evidence for alternate service delivery models to meet the growing need in cancer care, is generating evidence on contextual barriers and facilitators to promote effective implementation of these models into different clinical environments and different patient populations as appropriate.

Alternate service delivery models

Adopting alternate service delivery models for genetic counseling has the potential for improving access to services, may help reduce disparities in healthcare, and ultimately help achieve the promise of genomic medicine related to cancer care. Current alternate service delivery models for genetic counseling include broadly: alternate technology models, alternate visit models, and direct access testing models. Another alternative model more aptly described as a telementoring model, may address the immediate concern that the workforce shortage of genetic counselors is not expected to reach equilibrium until around 2024. The Extension for Community Healthcare Outcomes (ECHO) model uses telemedicine concept to create communities of practice where specialists work with local providers to manage patients by moving knowledge rather than individual patients and empowering other providers to deliver ongoing high quality care.

It is also likely regarding these alternate service delivery models that one size does not fit all at the


The demand for genetic counseling services and the need for alternate service delivery models to meet this demand in cancer care is continually growing. Models exist, however, there is little evidence on which models work best for which individuals or healthcare systems. Implementation science offers the tools to address this gap and evaluate such models in context for broader impact to integrate these models into cancer care delivery.

Key Words: genetic counseling, alternate genetic service models, implementation science, cancer genetic counseling

Address correspondence to Dr. Alanna Kulchak Rahm, Genomic Medicine Institute, 100 N. Academy Avenue, MC-26-20, Danville, PA 17822 USA
patient level, provider level, or the system level. Patient uptake of services and satisfaction may improve when allowed to choose how they receive genetic counseling. Likewise, the ability for organizations to implement alternate delivery models differs depending on factors such as provider acceptance, workflows, resources, and other internal and external factors.

Implementation science

The use of implementation science in cancer care has grown in the recent decade, as evidenced through many initiatives led by the National Cancer Institute, most notably the Cancer Moonshot, and has gained prominence in professional organizations such as the American Society of Preventive Oncology and the American Society of Clinical Oncology. Implementation science broadly is the study of integrating research findings into healthcare policy and practice. In the case of alternate genetic counseling service delivery models in cancer genetics, utilizing implementation science helps to generate evidence for broader impact by providing tools to consider context, multi-level complexity (patients, providers, and system level issues), and promotes real-world feasibility and functionality. Using tools from implementation science we can design studies of alternate service delivery models in context of the healthcare system and populations and learn which model works best for who under what conditions at the patient level, and what model works best for which system based on available resources and other factors. Implementation science provides multiple frameworks, theories, and models to guide the design, implementation, and evaluation of alternate delivery models in the context of care delivery settings. Key outcomes such as implementation outcomes, program outcomes, patient outcomes, and provider outcomes should be considered. Because alternate service models may work differently for different individuals or be more effective in different organizations or populations, it is critical to include these outcomes when designing and reporting on studies of alternative service delivery models.

As the need for alternative genetic service models grows due to the continued expansion and integration of genomic information in cancer care, it will be important to evaluate these models in the context of the various care delivery settings and populations that make up the US healthcare system today. Using the tools from implementation science we can better understand for whom different models work best and which models may be most effectively implemented to improve patient care in different clinical settings and populations to improve patient outcomes.

Disclosure

Dr. Alana Kulchak Rahm has no disclosures.

References

Genetic education and practice considerations of non-genetic providers

Veda N. Giri, MD
Departments of Medical Oncology, Cancer Biology and Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA


Germline testing for inherited prostate cancer is revolutionizing prostate cancer treatment for advanced and metastatic disease and is beginning to inform management for early-stage disease as well as prostate cancer screening discussions. Increasingly, non-genetic providers are performing genetic testing in their practices, necessitating focused efforts to address genetic education and working knowledge of genetic testing for responsible delivery of testing to men with or at risk for prostate cancer.

Key Words: prostate cancer, genetic testing, germline testing, provider education

Germline genetic testing is being increasingly performed for men with prostate cancer as well as men at risk for prostate cancer.1 Multiple genes have been reported to contribute to prostate cancer with varying risk estimates such as BRCA2, BRCA1, HOXB13, CHEK2, DNA mismatch repair genes, and ATM.2,3 Some of these genes, such as BRCA2, BRCA1, and ATM, are also associated with aggressive prostate cancer and poor outcomes.2,5 National guidelines have significantly expanded to include germline testing for all men with metastatic prostate cancer, men with high-risk disease, men with early-stage/low-risk disease based upon pathology and family history, and Ashkenazi Jewish ancestry.6,7 This expansion of genetic testing has led to an increasing demand for genetic counseling of men with prostate cancer, leading to difficulty with timely access to genetic testing.

Many non-genetic providers, such as urologists, oncologists, and primary care providers, have begun to perform germline testing in their own practices, raising the need to address appropriate pretest informed consent and post-test discussion and genetic recommendations for patients. A survey of prostate cancer providers in the Philadelphia region in 2017-2018 (n = 56) revealed that 14% of providers always consider genetic testing of their patients with prostate cancer, and 50% sometimes consider testing.8 Furthermore, survey results revealed that 65% felt cancer inheritance was important to discuss, 60% discussed the types of genetic test results to expect in the pretest discussion, 55% felt it necessary to discuss the familial cancer risk implications, and 45% responded it was important to discuss the genetic discrimination laws.8 A multi-institutional survey of academic oncologists (n = 26) revealed that 16/26 (62%) of oncologists reported taking conducting their own genetic education and testing of their patients with prostate cancer.9 Furthermore, most of the tests ordered were comprehensive or large cancer panels.9 Given the growth of genetic testing occurring in non-genetic practices, providers need to be aware of discussion elements for pretest informed consent for men with prostate cancer based upon best practice and as endorsed by multiple professional organizations.10-15 Furthermore, knowledge of genetic test results, recommendations, and implications for men and their families is important for non-genetic providers to impart to their patients once genetic test results return.1,5,7

Address correspondence to Dr. Veda N. Giri, MD, Thomas Jefferson University, 1025 Walnut Street, Suite 1015, Philadelphia, PA 19107 USA

© The Canadian Journal of Urology™: International Supplement, October 2019
Key areas of working knowledge, discussion with patients, and responsibilities of providers conducting genetic testing include:

- Knowledge of cancer inheritance, genetic testing considerations, and implications of test results.
- Understanding of mutations in key genes relevant to precision therapy, precision management, and prostate cancer screening.
- Identification of men meeting criteria for genetic evaluation based upon personal and family history.
- Discussion of cancer inheritance, family history intake, genetic test options, benefits/limitations of genetic testing, types of results, GINA law.
- Understanding which lab to choose for quality and experienced genetic testing.
- Consideration of men’s psychosocial needs when making a decision for genetic testing.
- Discussion of genetic results and recommendations based on test results and family history.
- Understanding of variant reclassification and follow up with patients.
- Facilitating cascade testing or further genetic evaluation for families.

Close collaboration between genetic and non-genetic providers is needed to address the genetic evaluation needs of men with prostate cancer and their families.

Disclosures

Dr. Veda N. Giri has no disclosures.
Considerations of germline testing in prostate cancer screening

Thomas J. Polascik, MD, Hazem Orabi, MD, on behalf of the Duke Cancer Institute Prostate Cancer Screening Collaborative
Division of Urology, Duke Cancer Institute, Durham, North Carolina, USA


Prostate cancer screening remains controversial in the medical field. While screening men above 50 years can impose overdiagnosis and overtreatment, targeted screening of males with pathologic variants of genetic mutations is evolving and viewed as sensible. Identifying such patients requires genetic testing in males having family history of prostate cancer or certain ethnicity. Such strategies will likely occur as routine practice once favorable results of ongoing studies assessing genetic predisposition are released.

Key Words: germline mutations, prostate cancer, prostate cancer screening, BRCA1, BRCA2, genetic testing

Hereditary prostate cancer (HPC), with approximately 10% incidence among prostate cancer patients, is defined by having ≥ 3 first-degree relatives within the same family or three successive generations or two first-degree relatives < 65 years with prostate cancer.1 Familial prostate cancer, with incidence of 25%, is considered with a history of prostate cancer in the family but not meeting the criteria of HPC.2 Both groups presage more aggressive disease and higher cancer-specific mortality than those without family history. The principal difference between those groups is the presence of inherited genetic mutations such as BRCA1/2 among HPC. As such, HPC has increased risk of secondary primary malignancies such as male breast, pancreatic and colon cancers. When prostate cancer was detected in patients with prostate cancer family history, nearly half in the early PROFILE study had normal PSA < 3 ng/mL.3

In prostate cancer, the percentage of patients with germline mutations differ according to disease stage, ranging from 4.6% (localized) upwards of 11.8% to 16.2% (metastatic).4,5 Mutations include BRCA1/2, FANC, ATM, PALB2, NBN, MRE11, BLM, and ATR. BRCA1/2 are the most commonly tested and identified associated with prostate cancer. BRCA2 and BRCA1 mutations are identified in 5.3% and 0.9 % with metastatic prostate cancer, respectively.4

Clinical trials are investigating the genetic predisposition to prostate cancer in individuals with family history and certain ethnicity, such as IMPACT, PROFILE and BARCODE 1. In the IMPACT study (ClinicalTrials.gov NCT00261456), prostate cancer detection rates during the initial year of screening were 2.3% for BRCA1 carriers and 3.3% for BRCA2 carriers.6 The low cancer detection rate was attributed to the limited number of men who had biopsies performed before the widespread adoption of mpMRI and fusion biopsies. The pilot PROFILE study (ClinicalTrials.gov NCT02543905) that included 100 males with family history of prostate cancer, showed a 25% cancer detection rate,7 a higher rate than IMPACT since all subjects underwent prostate biopsy irrespective of PSA level. Another PROFILE study (NCT02543905) is recruiting 700 individuals with family history of prostate cancer. The BARCODE 1 study (ClinicalTrials.gov NCT03158922) will evaluate the genetic profile using 170 prostate cancer risk single-nucleotide polymorphisms (SNPs) in men with genetic susceptibility. Men in the top 10% risk score will undergo prostate biopsy.
Genetic testing incorporated into routine prostate cancer screening can have a plethora of benefits for the patient and family. Detectable mutations of BRCA1/2 will facilitate targeted screening with early diagnosis and treatment before cancer advances. It may impact treatment options for patients requiring platinum-based chemotherapy or PARP-1 inhibitors. Moreover, it encourages screening for other primary cancers such as colon and pancreas, possibly initiating preventive strategies for yet unaffected organs. It will alert other family members to screen for breast and ovarian cancer and potentially offer early treatment with better prognosis and quality of life.

Current NCCN guidelines recommend genetic testing for all patients with metastatic, regional, very high-risk disease, or high-risk prostate cancer regardless of family history. Those genes include BRCA1, BRCA2, ATM, PALB2, and FANCA.7 There is no consensus yet regarding prostate cancer screening for carriers of pathogenic germline mutations as we await ongoing studies. However, it is recommended that prostate cancer screening in carriers commence at age 40-45 with annual PSA and DRE, utilizing age-adjusted PSA cutpoints. If PSA is above the upper limit, PSA is retested in 6-12 months; if increased, mpMRI/TRUS-biopsy is advised.

Although genetic testing has appeal, there are recognized limitations. Genetic testing is offered to those with strong family histories of prostate, breast or ovarian cancer according to contemporary guidelines. However, germline mutations such as BRCA1/2 have been detected in individuals lacking family history. Most genetic studies focus on detection of BRCA1/2 while less prevalent mutations such as CHEK2, MLH1, MSH2, MSH6, PMS2 are ignored. Lack of ample genetic counsellors, insurance coverage and defined follow up plans also remain challenges.

Several predictive instruments have been developed to better identify individuals with higher probability of germline BRCA1/2 mutations. The Manchester scoring system is a mathematical model that is more sensitive to BRCA2 mutations, taking into consideration cancer type and age at diagnosis. Additional optimization and refinements are required to identify people eligible for genetic testing. PSA and PSA velocity may not be sufficient for cancer screening in high-risk patients having genetic mutations as seen in IMPACT and PROFILE. mpMRI and novel prostate cancer markers could be an additional screening tool to detect high-risk prostate cancer at early stages.

At Duke University, we developed and implemented an EHR-embedded, risk-stratified prostate cancer screening algorithm as a clinical decision support tool in a primary care network, screening 49,980 in the first year. We implemented system-wide screening, incorporating, age, race, family history and genetic risk in a single health care system. Future efforts will incorporate more robust genetic testing in high-risk men as evidence becomes available.

Disclosures

The authors have no disclosures.

References

Germline testing for prostate cancer prognosis: implications for active surveillance

Brian T. Helfand, MD, PhD, Jianfeng Xu, MD, DrPH
Program for Personalized Cancer Care and Division of Urology, NorthShore University HealthSystem, Evanston, Illinois, USA

Based upon an evidence-based review of recently published manuscripts including our own studies, we first review germline variants that are significantly associated with prostate cancer aggressiveness and progression. We then discuss the clinical implication of germline variants in predicting grade reclassification of prostate cancer patients undergoing active surveillance. Finally, based on currently available evidence, we propose a working recommendation of germline testing and corresponding clinical management for localized prostate cancer patients, including those undergoing active surveillance.

Key Words: high penetrance genes, prostate cancer, germline

Introduction

Prostate cancer is recognized as one of the most heritable cancers.1 While family history is traditionally used as an indirect measurement of inherited risk, common prostate cancer risk-associated single nucleotide polymorphisms (SNPs) and rare pathogenic mutations in a number of genes make it feasible to directly measure genetic risk.2,3 Despite this progress, several major challenges exist in implementing germline testing. The first is a lack of understanding among many clinicians on the utility of germline testing for guiding prostate cancer screening, diagnosis and treatment. The second relates to an inability to distinguish three purposes of germline testing: predicting prostate cancer risk among unaffected men, predicting prognosis at time of prostate cancer diagnosis, and predicting treatment response of hormonal and targeted therapy. The third is lack of consensus on what genetic variants (common SNPs and rare mutations) are suitable for these different purposes. These challenges are exacerbated in the multigene panel-test era where 14 genes (ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, and TP53) are typically included in commercially available panels. This article will specifically focus on the second purpose of germline testing for predicting prostate cancer prognosis and its implication for active surveillance.

Genetic variants for prostate cancer prognosis

More than 160 prostate cancer risk-associated SNPs have been discovered.2 Together these SNPs have a strong cumulative effect, which can be measured by polygenic risk score (PRS). PRS has been consistently demonstrated as a powerful tool for predicting prostate cancer risk among unaffected men.2 However, its utility in predicting aggressiveness and prognosis is unclear at this stage.

In contrast to common SNPs, rare pathogenic mutations in several genes, especially DNA damage repair genes, have been reported to be associated with prostate cancer risk, aggressiveness/progression, and response to hormonal and targeted therapy.3,5 Although pathogenic mutations in many of these genes have been reported in advanced prostate cancer patients, it is important to note that observation of
these mutations in prostate cancer patients with clinically significant disease alone is not sufficient to implicate them as prognostic markers. Statistical evidence is required; especially in well-designed studies where phenotypes are well characterized, and sequencing/annotation methodologies as well as racial and ethnic background are comparable between groups of prostate cancer patients.

To date, significantly different frequencies of pathogenic mutations within BRCA2 and ATM have been consistently reported among men diagnosed with high-grade tumors and those who progressed to metastatic and lethal disease.\(^7,^6\) Evidence for pathogenic mutations of BRCA1 as a prognostic marker is weaker. A meta-analysis estimated that the risk of pathogenic mutations of BRCA1 for prostate cancer-specific death was 1.06, \(p = 0.90\) (in comparison, the same meta-analysis estimated that the risk for BRCA2 was 2.63).\(^7\) Evidence remains controversial for CHEK2 (all pathogenic mutations and the founder mutation, 1100delC).\(^8\)

In our recent study comparing pathogenic mutations among 1,694 prostate cancer patients who underwent radical prostatectomy at Johns Hopkins Hospital, including 706 patients with high-grade [Gleason grade (GG) 4 and 5] and 988 patients with low-grade disease (GG1), we documented that the frequency of germline pathogenic mutations in the above mentioned 14 genes was significantly higher in high-grade patients (8.64%) than low-grade patients (3.54%, \(p = 9.98 \times 10^{-9}\)). However, at the individual gene level, significant differences were found for only three genes: ATM (2.12% and 0.20%, respectively, \(p = 9.35 \times 10^{-6}\)), BRCA2 (2.55% and 0.20%, respectively, \(p = 8.99 \times 10^{-6}\)), and MSH2 (0.57% and 0%, respectively, \(p = 0.03\)). Higher but not statistically significant mutation frequencies in high-grade versus low-grade were found for BRCA1 (0.28% and 0.10%, respectively, \(p = 0.65\)) and CHEK2 (1.27% and 1.01%, respectively, \(p = 0.65\)). The estimated carrier rate was the same (0.71%) for HOXB13 G84E between the two groups. Our study highlights the challenge to obtain statistical evidence for rare pathogenic mutations.

Recent data on germline mutations for predicting active surveillance outcomes

Based on the above data, we tested the hypothesis that mutation carriers of men undergoing active surveillance have worse outcomes in two active surveillance cohorts at NorthShore University HealthSystem and Johns Hopkins.\(^9\) Of these 1,211 prostate cancer patients, mutation carriers in a three-gene panel (BRCA2, ATM, and BRCA1) were more likely to experience grade reclassification (11 of 26 carriers, 42.31%) than non-mutation carriers (278 of 1,185 non-carriers, 23.45%, \(p = 0.04\)). The results were strongest for BRCA2. It is recognized that the results should be validated since the number of pathogenic mutation carriers was relatively low.

Recommendation of germline testing for localized prostate cancer patients

To reduce confusion, we propose that germline testing be offered for predicting prognosis to all prostate cancer patients at the time of diagnosis, including low-grade patients considering active surveillance. Furthermore, since most mutation carriers do not report a FH, we propose that germline testing be offered regardless of FH. Based upon available evidence of individual genes at this stage, pathogenic mutations may be classified in four prognostic groups: ‘actionable’ for BRCA2 and ATM, ‘uncertain’ for BRCA1, CHEK2 and MSH2, ‘not actionable’ for HOXB13, and ‘lack of sufficient data’ for the remaining genes.

Disclosures

Dr. Brian T. Helfand is a speaker for Ambry Genetics. Dr. Jianfeng Xu has no disclosures.

References

Germline testing for prostate cancer: community urology perspective

Raoul S. Concepcion, MD,1,2
1Department of Urology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA
2Urology Division, Integra Connect, West Palm Beach, Florida, USA


In an attempt to better understand how community urology practices would begin to incorporate hereditary testing in prostate cancer patients, we developed an eight-question online survey to identify current testing patterns, utilization of genetic counseling and barriers that practices face. Fifty-two large community urology practices participated. A total of 32/52 (63%) of the responders were already offering testing to select patients. The big hurdles practices were concerned when initiating testing were fear of medical/legal liability (22%), concerns over reimbursement and out of pocket patient expense (20%) and the complexity, time and difficulty to enter a complete family history/pedigree into the EHR (18%).

Key Words: germline testing, community urology practices

Akin to many industries in the United States and independent of each other during the 1990's, there was consolidation and merging of community urology groups in various markets across the country. As a result of these trends, a notable proliferation of large single specialty urology practices began to surface across the U.S.1 And with federal regulations and statutes that are still in existence today (https://www.auanet.org/advocacy/comment-letters-and-resources/in-office-ancillary-services-exception/preserve-the-ioase-exception-to-the-stark-law), integrated services, including anatomic pathology, laboratory services, ambulatory surgery centers, radiation centers and dispensing pharmacy capabilities, could now be potentially housed under a single practice, resulting in more efficient and cost effective care.2 Consequently, many of these entities, some of which may number up to 100 urologists under a single provider number, are diagnosing hundreds of new prostate cancer cases and managing thousands of existing prostate cancer patients, at various stages of the disease, annually. In conjunction with these large volume of cases, regardless of the disease state, that exist within a single practice, sub-specialization within the groups also began to emerge in an attempt to enhance care and optimize outcomes.

One of the early service lines developed was the incorporation of advanced prostate clinics within the practice, which was a direct result of the rapid approvals of many agents during the early part of this decade for the treatment and management of metastatic castration resistant prostate cancer (mCRPC).3 Because of this paradigm shift away from urologists managing only localized disease and transitioning to caring for the patient across the disease spectrum, it becomes necessary and a mandate for groups that have adopted this philosophy to provide services and testing that will facilitate this culture of providing continuity of care. With the recent discoveries that lethal prostate cancer may have a germline component4 and that men with mCRPC who have been heavily treated with multiple agents may develop somatic DNA repair gene mutations,5 it is incumbent on the urology practices to have a thorough understanding of who are candidates that require testing and how to incorporate this into a busy clinical setting.

Address correspondence to Dr. Raoul S. Concepcion, 905 20th Avenue South, N1310, Nashville, TN 37203 USA
However, there are many obstacles that community urology practices face when trying to operationalize a new service line that is not readily inherent to their surgical practice. These potential hurdles, specific to hereditary testing, include:

1. Fear of medical/legal liability if mutations are discovered and are not addressed with the patient or family members.
2. Lack of certified genetic counselors in the immediate area.
3. Concerns over reimbursement and potential out of pocket expense to the patient.
4. Lack of education/awareness of somatic vs. germline testing.
5. Complexity, time involved and difficulty in entering family history/pedigree into the electronic health record (EHR).
6. Lack of education/understanding of the various genes that are associated with increased risk or disease progression.

Given the clinical significance that hereditary testing potentially represents for high risk prostate cancer patients, their families and the potential large volume of these patients within a single practice, we need a better understanding of which factors are resulting in under testing of appropriately identified patients. Knowing that there is marked variability in the organizational and daily operational structure of large urology groups, we devised an eight-question survey to help interrogate this issue. The survey was posted online and hosted by Integra Connect (West Palm Beach, FL, USA). Emails were sent to members of LUGPA (Chicago IL, USA), a not for profit entity that represents the interest of independent urologic practices in the United States, inviting them to take part in the survey. A total of 52/149 (34.9%) responded to the online survey. Key findings from the survey:

1. Representation of respondents had group size of 0-10, 11-25, 26-50, > 50 providers in the practice of 25%, 33%, 29% and 13% respectively.
2. 21/52 (40%) of the respondents had > 500 newly diagnosed cases per practice in 2018.
3. Cumulatively, a total of 154,640 unique prostate cancer patients (defined by at least 1 office visit based on ICD 10 and CPT code) were seen in these 52 practices in 2018.
4. 48/52 (94%) of the respondents were aware of the most recent SUO policy statement on hereditary testing in prostate cancer.
5. 32/52 (63%) of the respondents were already offering hereditary testing to their patients
6. 33/52 (65%) of the respondents had access to genetic counseling within a 20 mile radius of their office location.
7. Fear of medical/legal liability (22%), concerns over reimbursement and out of pocket patient expense (20%) and the complexity, time and difficulty to enter a complete family history/pedigree into the EHR (18%) were the three most commonly cited issues that concerned the respondents when implementing or considering a hereditary testing program.

Conclusion

Based on a sampling of 52 large community urology practices geographically distributed across the United States, 94% of the practices are currently aware of the recent SUO policy statement. 63% of the groups had already incorporated testing for select patients and another 25% in the active process of developing an in house testing program. The primary practice concern for offering and initiating a hereditary testing program is the fear of medical/legal liability if mutations are identified but not addressed with the patient and/or family. Given the large volume of prostate cancer patients diagnosed and managed by these large groups, we hope this will increase utilization in appropriately identified patients.

Acknowledgement

A special thanks to Invitae Corporation for providing an unrestricted educational grant to support this initiative.

Disclosures

Dr. Raoul S. Concepcion is a consultant for Dendreon, Integra Connect, Cellay, Invitae, Merck, Pfizer, Astellas, Janssen, Sun Pharma, CUSP and Clovis.

He is a speaker for Astellas, Pfizer, Amgen and Sun Pharma.

References


© The Canadian Journal of Urology™; International Supplement, October 2019
Genetic counseling perspective of engagement with urology and primary care

Colette Hyatt, MS, LCGC, Jessica Russo, MS, LCGC, Carey McDougall, MS, LCGC

Thomas Jefferson University, Philadelphia, Pennsylvania, USA


Germline genetic testing for prostate cancer is helping to inform risk stratification and staging of prostate cancer and also screening for men with family history of prostate cancer. Genetic counseling is an important piece of germline genetic testing; however there can be limitations of access to genetic counselors and other genetic professionals. It is important to integrate genetic counseling with urology and primary care practices.

Key Words: genetic counseling, genetic testing, primary care, urology, prostate cancer

Prostate cancer is a common cancer that also has a high hereditary component. Studies have shown 15% to 17% of men with prostate cancer have a germline mutation regardless the stage of prostate cancer. Germline mutations are reported in 12% of men with metastatic prostate cancer. The National Comprehensive Cancer Network (NCCN) recommends that family or personal history of high-risk germline mutations be included in considerations of prostate cancer screening. Given that men with BRCA1 and BRCA2 germline mutations have an increased risk of developing prostate cancer at an earlier age with higher mortality rates, it is discussed that PSA screening should start at age 40 with consideration of annual screening intervals.

After an initial prostate cancer diagnosis, germline genetic testing is important in risk stratification and staging. The NCCN also discusses asking about high-risk germline mutations and family history. Germline genetic testing is recommended for individuals with a strong family history, a high or very high-risk prostate cancer, or intraductal histology.

Active surveillance is often recommended for very low-risk, low-risk, and favorable intermediate-risk prostate cancer depending on other factors such as life expectancy. However, men with prostate cancer and BRCA1 or BRCA2 germline mutation may have an increased risk of progression on local therapy and decreased overall survival.

The NCCN also recommends that, prior to genetic testing, an expert in cancer genetics provide pretest genetic counseling. Pretest genetic counseling includes, collecting a three generation family history, evaluating who is best to test in the family, determine which genetic testing would be best for the patient and/or their family, educating on possible genetic testing results, and addressing privacy/psychosocial implications. Genetic counselors (GCs) play an important role of ensuring patients are properly consented to genetic testing.

However, there are limitations to access to GCs and genetic professionals. Many men who meet genetic testing criteria will see their urologist and primary care doctor, but do not have access to a GC. Common barriers to this access include hardship for patients to travel to another appointment and long wait times at genetics clinics. Limitations in access to genetic testing can restrict men from obtaining vital information regarding their cancer screening and treatment.
a urology group or primary care office considers genetic testing in their office, it is important to consider a few challenges that might occur with genetic testing.

A considerable challenge in the genetic testing process is obtaining accurate family history information. GCs take a comprehensive family history by a medical pedigree, which is a graphic representation of an individual’s family history. They ask questions to determine family history of cancer and obtain a three-generation representation of the family. It is important for the pedigree to be as accurate as possible. When possible, family history should be confirmed with a pathology report or doctors’ note. The time it takes to gather a complete pedigree varies between patients, however it is a very detailed process. Taking a family history is also very personal and brings up psychosocial concerns. Family history information is used to help guide which genetic test is ordered, screening recommendations for family members, and interpretation of genetic testing results. The amount of time spent with patients is 9 to 16 minutes for urologists and 13 to 24 with family medicine doctors. A detailed family history would be difficult to get in that amount of time with other concerns a urologist or primary care physician will need to address. GCs spend around 60 to 90 minutes with a new patient.

Genetic counseling also includes a thorough discussion of the possible results and the implications on cancer risk. Results of genetic testing may not always be clear. Variants of uncertain significance (VUS) are reported in about 30% of men with prostate cancer who have undergone genetic testing. A VUS may not affect recommendations at the time of reporting; however it can cause confusion and a lack of understanding for the patient as well as providers. In addition, testing using a large panel can uncover mutations in genes with unexpected or ambiguous cancer risks. Pretest genetic counseling may aid in addressing the possibility of these ambiguous or unexpected results.

How do we improve access to genetic counseling for patients without overwhelming already busy providers? Offices will need to determine which patients can be consented in the office or which patients need a GC appointment. The key is to ensure patients are fully consented and are prepared for the information it will provide. Providers also need to ensure they have the correct family history information to interpret these results. A collaborative approach with GCs and primary care and urology offices will ensure patients are being properly consented, receiving the right testing and getting this information in an easy and timely way.

Disclosures

Carey McDougall and Jessica Russo have no disclosures. Colette Hyatt is a consultant for GenomeSmart.

References


© The Canadian Journal of Urology™: International Supplement, October 2019
Genetically-informed treatment for advanced and metastatic prostate cancer

Alicia K. Morgans, MD, MPH, Brittany M. Szymaniak, PhD, CGC

Department of Hematology and Oncology, Northwestern University, Chicago, Illinois, USA


The landscape of genetic testing for prostate cancer is rapidly evolving. There is increasing evidence that individuals with germline mutations in DNA-repair genes are more responsive to targeted therapies. Due to potential implications for treatment, these genes should be taken into consideration when determining the scope of genetic testing.

Key Words: genetic testing, treatment decision making, prostate cancer

Introduction

Germline genetic testing is a critical aspect of care for men with metastatic prostate cancer. Consensus guidelines include recommendations for consideration of genetic counseling and testing for all men with metastatic prostate cancer, and men with high-risk localized prostate cancer with a family history.\(^1,2\) Despite this guidance, there are multiples challenges in appropriately implementing these recommendations, especially given inconsistent insurance coverage for testing, limited number of genetic counselors, and busy clinical work-flows. We review an evolving list of genes that are highest priority for identification in treatment decisions for prostate cancer.

Prioritizing genes of interest

There is increasing evidence that individuals with mutations in genes involved in homologous recombination (HR) or mismatch repair (MMR) pathways may drive cancers that are sensitive to treatments targeting these deficiencies. The rate of alterations exceeds 10% in men with metastatic prostate cancer.\(^3\) BRCA2 mutations account for the majority of hereditary prostate cancer cases, but other gene mutations also occur commonly.\(^4\) These mutations may confer sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitor or checkpoint (CP) inhibitor therapies, Table 1.

Homologous recombination

Mateo et al assessed the effectiveness of olaparib in metastatic castration-resistant prostate cancer (mCRPC) in the TOPARP-A trial, a phase 2 trial including 50 men who underwent biopsies and next generation sequencing to characterize germline and
**TABLE 1. Proposed prioritized list of genes to test to inform treatment of men with advanced or metastatic prostate cancer**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein function</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Ser/Thr protein kinase involved in repair of DNA double strand breaks (DSB)</td>
<td>PARP</td>
</tr>
<tr>
<td>ATR</td>
<td>Ser/Thr protein kinase that acts as a DNA damage sensor</td>
<td>PARP</td>
</tr>
<tr>
<td>BARD1</td>
<td>Heterodimerizes with BRCA1 to mediate DNA damage response and repair</td>
<td>PARP</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Phosphoprotein that assists in repairing DSBs</td>
<td>PARP</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Phosphoprotein that promotes binding RAD51 onto single-stranded DNA for repair</td>
<td>PARP</td>
</tr>
<tr>
<td>BRIP1</td>
<td>DNA-dependent ATPase and 5' to 3' DNA helicase required for the maintenance of chromosomal stability</td>
<td>PARP</td>
</tr>
<tr>
<td>CDK12</td>
<td>Cyclin-dependent kinase that regulates expression of genes involved in DNA repair</td>
<td>PARP</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Ser/Thr protein kinase required for activation of repair in response to DSBs</td>
<td>PARP</td>
</tr>
<tr>
<td>EPCAM</td>
<td>Antigen that can upregulate c-myc, e-fabp, and cyclins A&amp;E; mutations can disrupt MSH2 expression</td>
<td>CP</td>
</tr>
<tr>
<td>ERCC3</td>
<td>ATP-dependent 3'-5' DNA helicase involved in nucleotide excision repair of damaged DNA</td>
<td>PARP</td>
</tr>
<tr>
<td>FAM175A</td>
<td>Binds RAP80 and BRCA1 to target sites of DNA damage</td>
<td>PARP</td>
</tr>
<tr>
<td>(ABRAXAS1)</td>
<td>Fanconi Anemia pathway proteins respond to interstrand cross-links</td>
<td>PARP</td>
</tr>
<tr>
<td>GEN1</td>
<td>Nuclease that resolves intermediate DNA structures that form during homologous recombination and DSB repair</td>
<td>PARP</td>
</tr>
<tr>
<td>HDAC2</td>
<td>Responsible for the deacetylation of lysine residues on the N-terminal part of the core histones</td>
<td>PARP</td>
</tr>
<tr>
<td>MLH1</td>
<td>Heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative CP DNA MMR system</td>
<td>PARP</td>
</tr>
<tr>
<td>MLH3</td>
<td>Member of the MutL-homolog (MLH) family of DNA MMR genes</td>
<td>CP</td>
</tr>
<tr>
<td>MRE11</td>
<td>Component of the MRN complex that plays a central role in DSB repair</td>
<td>PARP</td>
</tr>
<tr>
<td>MSH2</td>
<td>Forms two different heterodimers (MSH2-MSH6 and MSH2-MSH3 heterodimers) that bind DNA mismatches</td>
<td>CP</td>
</tr>
<tr>
<td>MSH6</td>
<td>Heterodimerizes with MSH2 to form MutS alpha, which binds to DNA mismatches</td>
<td>CP</td>
</tr>
<tr>
<td>NBN</td>
<td>Component of the MRN complex that plays a central role in DSB repair</td>
<td>PARP</td>
</tr>
<tr>
<td>PALB2</td>
<td>Recruits BRCA2 and RAD51 to DNA breaks</td>
<td>PARP</td>
</tr>
<tr>
<td>PPP2R2A</td>
<td>Ser/Thr phosphatases implicated in the negative control of cell growth and division</td>
<td>PARP</td>
</tr>
<tr>
<td>PMS2</td>
<td>Heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative CP DNA MMR system</td>
<td>PARP</td>
</tr>
<tr>
<td>RAD50</td>
<td>Component of the MRN complex that plays a central role in DSB repair</td>
<td>PARP</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Involved in the homologous recombination repair pathway of DSB breaks</td>
<td>PARP</td>
</tr>
<tr>
<td>RAD51D</td>
<td>Involved in the homologous recombination repair pathway of DSB breaks</td>
<td>PARP</td>
</tr>
<tr>
<td>RAD54L</td>
<td>Functions in the recombinational DNA repair pathway</td>
<td>PARP</td>
</tr>
</tbody>
</table>

PARP = poly ADP ribose polymerase inhibitor; CP = checkpoint inhibitor

Somatic mutations related to DNA damage repair and potential sensitivity to PARP inhibition. Out of the 49 patients evaluated for response, 16 had tumor aberrations in DNA-repair genes; mutations were identified in ATM, BRCA1, BRCA2, CHEK2, FANCA, HDAC2, MLH3, MRE11, NBN, and PALB2. Participants
Genetically-informed treatment for advanced and metastatic prostate cancer

with DNA-repair mutations were more responsive to olaparib, with 14/16 (88%) meeting criteria for a response (reduction in tumor size by standard RECIST criteria, a decline in PSA, and a reduction in circulating tumor cell count), versus 2/33 (6%) without mutations.

The recently presented TOPARP-B trial included patients with mCRPC after progression on at least one line of taxane therapy, who were pre-selected for germline or somatic HRD mutations. They were treated with olaparib in two formulations to assess response to therapy, robustness of the response based on dose, and the toxicity profile. The response rate among patients with HRD mutations varied by gene, with BRCA2 carriers having an 80% response rate, and a median radiographic PFS of 8 months. Patients with PALB2 mutations had a 57% response rate, while patients with ATM mutations had relatively mild responses (37%), but the durations were prolonged.

TRITON 2 (NCT02952534), is an open label phase 2 study evaluating rucaparib in patients with mCRPC and a germline or somatic mutation in an HRR gene, including BRCA1, BRCA2, CDK12, or ATM mutation. An interim report suggests that individuals with ATM mutations did not experience measurable response, suggesting that different PARP inhibitors may have differential effects by mutation. PROfound (NCT02987543), a phase 3 trial evaluating olaparib versus abiraterone or enzalutamide in mCRPC patients with HRD mutations, has reportedly met its primary endpoint of prolonging radiographic free survival, though specifics have not yet been reported.

Mismatch repair (MMR)
The role of immunotherapy in prostate cancer treatment is still being defined. The use of checkpoint inhibitors, such as pembrolizumab, is predominantly driven by identifying MMR alterations and microsatellite instability (MSI), as pembrolizumab is approved for any patient with MSI. The inclusion of prostate cancer on the spectrum of Lynch syndrome cancers has been controversial. However, due to the possible response from checkpoint inhibitors, germline testing for these MMR genes is often included as part of the germline testing, especially if there is a suggestive family history.

A recent single institution retrospective review by Tucker et al reported on the effectiveness of pembrolizumab in 48 men with heavily pretreated mCRPC. In this non-randomized study, 17% had a ≥ 50% PSA decline, and 8% had a PSA decline of ≥ 90% decline. Graff and colleagues reported a similar response rate in a study of 28 men with mCRPC progressing on enzalutamide; 18% experienced a ≥ 50% PSA decline when pembrolizumab was added to enzalutamide.

Conclusions
There will be increasing demand for genetic testing and counseling for men with prostate cancer as treatment options are expected to be approved in the near future. Part of rationally integrating testing into practice is ensuring that clinicians prioritize those genes most likely to affect treatment decisions and cascade testing for familial cancer syndromes. The genes identified in this review are an evolving list that should be considered when integrating germline and somatic mutation testing into clinical practice for men with prostate cancer.

Disclosures
Dr. Alicia Katherine Morgans received honoraria from Janssen, Astellas, AstraZeneca, Bayer, Sanofi, Seattle Genetics and research funding from Bayer. Dr. Brittany M. Szymaniak has no disclosures.

References
Genetic counseling and oncology: proposed approaches for collaborative care delivery

Jacquelyn Powers, MS, Kelsey Spielman, MS, Rebecca Mueller, MS, Melissa Batson, BS, Stacy Pundock, BS, Anna Arutyunova, BS, Heather Symecko, MPH, Susan Domchek, MD

University of Pennsylvania, Basser Center for BRCA, Philadelphia, Pennsylvania, USA


Demand for cancer genetic counseling has grown rapidly in recent years as germline genomic information has integrated into cancer care. There are currently an insufficient number of genetic counselors (GC) to address genetic testing need through traditional pre- and post-test counseling. Alternative genetic counseling frameworks, discussed here, are under study to increase access to genetic testing while optimizing the skillsets of existent master’s-trained GCs.

Key Words: genetic counseling, genetic testing, optimization, alternative delivery model

Demand for cancer genetic counseling has grown rapidly in recent years as germline genomic information has integrated into cancer care.1 There are particular cohorts in which a missed opportunity for genetic testing is a missed opportunity for the potential of a targeted therapeutic intervention.2 In particular, this is applicable to men with metastatic prostate cancer with germline BRCA1 or BRCA2 mutations as it relates to poly ADP ribose polymerase (PARP) inhibitors, or germline mismatch repair gene mutations as it relates to PD-1 inhibitors. The National Comprehensive Cancer Network (NCCN) has adapted genetic testing guidelines to support the recommendation to extend genetic testing to all men with metastatic prostate cancer regardless of family history3,4 and all those with regional disease.3

The traditional approach to the identification of individuals with genetic cancer susceptibility has been risk assessment and genetic testing under the provision of a specialist such as a genetic counselor (GC). This involves a pre- and post-test consultation in which the patient initially presents to a clinical genetics clinic for review of personal/family history, formulation of a differential diagnosis, facilitation of informed consent and specimen collection. The patient then returns to the clinic for results interpretation and medical management discussion; the latter often coupled with a physician. There are recognized benefits to the traditional model including improved patient satisfaction, adherence to cancer risk management, as well as documented cost savings for an institution.1 Furthermore, misinterpretation of test results, inappropriate medical management, and adverse psychosocial outcomes have been reported in the absence of adequate genetic counseling.5-7 This traditional framework is considered the standard of care by certain professional organizations;1 however, in oncological care, this framework is presently challenged by the growing need for genetic testing for therapeutic decision making and the limited GC workforce. This increased need has forced dialogue and the development of strategies for alternative approaches to genetic counseling (e.g. telegenetics, telephone counseling). The latter strategies designed to engage patients and increase GC access, while trying to optimize the skillsets of existent master’s-trained GCs.

Address correspondence to Jacquelyn Powers, 3400 Civic Center Blvd., 3W Perelman Center for Advanced Medicine (PCAM), Philadelphia, PA 19104 USA
Several centers have proposed different models of genetic evaluation of men with prostate cancer, Table 1. Some institutions have considered weighted involvement of the treating oncologist in pre-test education and GC involvement weighted toward post-test responsibilities. In order for such an approach to be successful providers should have proficiencies with the pre-test elements as listed in the subtext of Table 1 and implementation procedures must be in place in order to integrate into clinic practice flow. The challenges of insurance coverage and test costs, discerning optimal diagnostic testing laboratory (ies), variant reclassification and communication must be considered and balanced realistically with provider bandwidth. An additional hybrid approach is being run in parallel at two academic medical centers; the University of Pennsylvania (Penn) and Memorial Sloan Kettering Cancer Center (MSKCC). Patients with metastatic prostate cancer, through an IRB protocol, receive standardized pre-test education using a video and brochure by non-genetics provider. The primary endpoint is to evaluate the acceptability of an alternative care model, as measured by emotional distress and satisfaction with genetic testing decision and with genetic counseling (analysis underway). The research staff (RS) facilitates informed consent and biospecimen collection. Per protocol, the genetic test is preselected (14 gene panel) and testing is currently covered by the study. Penn and MSKCC GCs return results and provide post-test telephone counseling. This point of care testing yielded a nearly 9-fold increase in patients who underwent genetic testing in 2018 as compared to pre-protocol "traditional model" usual care in 2017, as well as a 7-fold increase in pathogenic/likely pathogenic variants identified. As this protocol continues, there will be modifications to address feasibility and sustainability such as cost responsibility and implementation without RS participation, while still relying on GCs for results interpretation, disclosure, and cascade testing, if applicable. Of note, in the absence of on-site GCs, most CLIA-CAP commercial diagnostic laboratories employ their own GCs to whom patients/providers may request telephone genetic counseling. Efficacy data is currently lacking when comparing the traditional versus alternative approaches.

Lastly, and in brief, automated tools are under development to scale delivery of genetic and genomic information. One example is HIPAA-compliant,
clinical grade chatbots (such as www.cleargenetics.com). Through inclusion and review from experts within the key medical communities, including GCs, there is potential for responsible delivery of automated approaches under well-defined clinical scenarios. Prior to standard clinical use, such approaches are best studied under IRB protocol. What remains consistent in clinical cancer genetics is the ever-changing landscape. Continued dialogue across oncology, urology, genetic counseling, as well as commercial laboratories, and direct-to-consumer companies is critically important to address the needs of men undergoing germline testing for inherited PrCa.9

Disclosures

Jacquelyn Powers received honoraria from Myriad Genetic Laboratories.
Kelsey Spielman, Rebecca Mueller, Melissa Batson, Stacy Pundock, Anna Arutyunova and Heather Symecko have no disclosures.
Dr. Susan Domchek received honoraria from AstraZeneca, Clovis Oncology, Bristol-Myers Squibb and research funding from AstraZeneca (Inst), Clovis Oncology (Inst), PharmaMar (Inst).

References
