VOLUME 36 · NUMBER 4 · FEBRUARY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

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Published at jco.org on December 13, 2017.

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0732-183X/18/3604w-414w/$20.00

ABSTRACT

Purpose
Guidelines are limited for genetic testing for prostate cancer (PCA). The goal of this conference was to develop an expert consensus-driven working framework for comprehensive genetic evaluation of inherited PCA in the multigene testing era addressing genetic counseling, testing, and genetically informed management.

Methods
An expert consensus conference was convened including key stakeholders to address genetic counseling and testing, PCA screening, and management informed by evidence review.

Results
Consensus was strong that patients should engage in shared decision making for genetic testing. There was strong consensus to test *HOXB13* for suspected hereditary PCA, *BRCA1/2* for suspected hereditary breast and ovarian cancer, and DNA mismatch repair genes for suspected Lynch syndrome. There was strong consensus to factor *BRCA2* mutations into PCA screening discussions. *BRCA2* achieved moderate consensus for factoring into early-stage management discussion, with stronger consensus in high-risk/advanced and metastatic setting. Agreement was moderate to test all men with metastatic castration-resistant PCA, regardless of family history, with stronger agreement to test *BRCA1/2* and moderate agreement to test *ATM* to inform prognosis and targeted therapy.

Conclusion
To our knowledge, this is the first comprehensive, multidisciplinary consensus statement to address a genetic evaluation framework for inherited PCA in the multigene testing era. Future research should focus on developing a working definition of familial PCA for clinical genetic testing, expanding understanding of genetic contribution to aggressive PCA, exploring clinical use of genetic testing for PCA management, genetic testing of African American males, and addressing the value framework of genetic evaluation and testing men at risk for PCA—a clinically heterogeneous disease.

J Clin Oncol 36:414-424. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Prostate cancer (PCA) is the third leading cause of cancer-related death in US men, accounting for 26,730 deaths in 2017.[1] There is increasing evidence that PCA has substantial inherited predisposition,[2,3] with higher risks conferred by *BRCA2* and *BRCA1* (associated with hereditary breast and ovarian cancer [HBOC] syndrome), and *HOXB13* (associated with hereditary prostate cancer [HPC]).[4-24] Furthermore, *BRCA2* mutations have been associated with poor PCA-specific outcomes.[9-13] There is also emerging evidence of the link between PCA

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.74.1173

DOI: https://doi.org/10.1200/JCO.2017.74.1173

and DNA mismatch repair (MMR) gene mutations (accounting for Lynch syndrome [LS]).[25-30] Furthermore, inherited genetic mutations are being uncovered in up to 12% of men with metastatic PCA, primarily in DNA repair genes such as *BRCA1*, *BRCA2*, and *ATM*,[31,32] with improved clinical outcomes by specific targeted agents.[33,34] Identifying genetic mutations of inherited PCA, therefore, has implications for cancer risk assessment for men and their families,[35,36] for precision treatment of metastatic disease,[33,34] and is being incorporated into guidelines for individualized PCA screening strategies specifically for male *BRCA1/2* mutation carriers.[35,37]

However, no centralized guidelines exist regarding genetic counseling and genetic testing for PCA or optimal use and interpretation of multiple genes now available on commercial PCA gene panels (Table 1).[38] At least three commercial laboratories have PCA multigene panels available that include *BRCA1*, *BRCA2*, *HOXB13*, DNA MMR genes, and multiple additional genes (such as *ATM*, *CHEK2*, and *NBN*; Table 1). Some of these genes provide actionable PCA risk information, whereas data for PCA risk is limited for other genes on these panels. Therefore, testing capability has created a dilemma regarding optimal application of genetic tests for counseling and evaluation of inherited PCA.

Genetic counseling is a dynamic process in which trained cancer genetic counseling professionals perform detailed intake of personal history and family cancer history, discuss genetic inheritance of cancer and genetic test options, address implications of genetic test results with patients and their families, and clarify patient preferences regarding genetic testing to make an informed decision for proceeding with testing.[39,40] However, guidelines are limited regarding genetic counseling and genetic testing for PCA (Table 2) and focus only on *BRCA1/2* testing. Current National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast and Ovarian (Version 2.2017) guidelines address *BRCA1/2* testing for men with a personal history of PCA limited to Gleason ≥ 7 and specific family history (FH) features.[35] An additional criterion for germline genetic testing is *BRCA1/2* mutation detected on somatic tumor testing.[35] Although these expert panel guidelines begin to address *BRCA1/2* testing for PCA, they exclude addressing other genes now available through multigene panels, several of which are implicated in PCA predisposition (Table 1).

Genetic testing has potential to inform PCA screening and targeted treatment, as exemplified in other cancers.[35,36,41] NCCN guidelines (Genetic/Familial High-Risk Assessment: Breast and Ovarian) state that PCA screening should begin at age 45 years for male *BRCA2* mutation carriers and to consider this recommendation for *BRCA1* carriers.[35] Current NCCN Prostate Cancer Early Detection Panel (Version 2.2016) agreed that men should be asked about the presence of known *BRCA1/2* mutations in their families.[37] The group added consideration of FH of *BRCA1/2* mutations to the baseline discussion of risks and benefits of PCA screening but believed that data are insufficient to change screening and biopsy recommendations.[37] Given increasing knowledge of genetic contribution to PCA (such as from *HOXB13* and DNA MMR genes) and expanding availability of commercial multigene panels (Table 1), there is a need for enhanced guidance on how multigene testing may be incorporated in PCA screening discussions.

Finally, precision medicine is catapulting the need for genetic testing to inform cancer treatment, particularly in the advanced-stage setting. Emerging studies report clinical activity of polyadenosine diphosphate-ribose polyermerase (PARP) inhibitors in metastatic PCA, particularly for men with DNA repair mutations.[33,34] Recent accelerated US Food and Drug Administration approval of immune checkpoint inhibitors for microsatellite instability-high and MMR-deficient cancers further highlights the increasing role of genetic testing in cancer treatment,[42] with implications for PCA. Thus, comprehensive guidance for multigene testing for inherited PCA is now critical for cancer risk, screening, and treatment implications.

Because multigene testing capability for PCA is now a reality, a consensus conference was convened to address the clinical genetic evaluation spectrum for inherited PCA. The Philadelphia Prostate Cancer Consensus 2017 was held in Philadelphia, Pennsylvania on March 3 and 4, 2017 and focused on the role of genetic testing for inherited PCA risk as well as genetic counseling, screening, and management on the basis of genetic findings. The conference was attended by stakeholders involved in PCA early detection, treatment, research, and patient advocacy. This was the first centralized, multidisciplinary conference, to our knowledge, focused on addressing and developing a working framework for the comprehensive genetic evaluation of inherited PCA in the multigene testing era.

Table 1. Current Genes on PCA Multigene Panels, Evidence Summary for PCA Risk, and Guidelines Available

Gene	Syndrome	Evidence Summary for Association to PCA Risk*	Guidelines for PCA Screening†
BRCA1	HBOC	A	x
BRCA2	HBOC	A‡	x
DNA MMR genes	LS	B	
HOXB13	HPC	A	
TP53	LFS	D	
ATM		C	
CHEK2		D	
PALB2		D	
NBN		C	
RAD51D		D	

NOTE. Adapted from Giri et al[38] to include consensus panel review. Detailed evidence review provided in Appendix Tables A2-A6.

Abbreviations: HBOC, hereditary breast and ovarian cancer; HPC, hereditary prostate cancer; LFS, Li-Fraumeni syndrome; LS, Lynch syndrome; MMR, mismatch repair; PCA, prostate cancer.

*Grade of evidence for PCA is summarized as follows: (A) High-grade evidence: At least one prospectively designed study or three or more large validation studies or three or more descriptive studies; (B) Moderate-grade evidence: two cohort or case-control studies; (C) Emerging data: increasing data in support of association to PCA, but not yet moderate-grade evidence; (D) Low/insufficient: limited data or not studied in the context of PCA.

†National Comprehensive Cancer Network High-Risk Assessment: Genetic/Familial Breast and Ovarian (Version 2.2017).[35]

‡High-grade evidence for association to lethal/aggressive PCA.

METHODS

Panel Members

The panel included 71 experts from the United States, Canada, England, and the Netherlands. Panel selection criteria included consideration of stakeholders with expertise in PCA early detection, treatment, genetic counseling, clinical cancer genetics, research, bioethics, and advocacy, along with patient advocates (Appendix Table A1, online only).

Table 2. Gaps in Genetic Evaluation of Inherited PCA Addressed by Consensus Criteria

Question	Current NCCN Guidelines	Consensus Criteria	Gaps Addressed by Consensus Criteria
Which men should be considered for genetic counseling and genetic testing?*	NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian (2.2017). An individual with a personal and/or family history of three or more of the following: breast, pancreatic, PCA (Gleason ≥ 7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, macrocephaly, hamartomatous polyps of GI tract	• Patients should engage in shared decision making for genetic testing for PCA (Consensus: 77%) • All men with PCA from families meeting established testing or syndromic criteria for the following should be considered for genetic counseling and testing: – HBOC (Consensus: 93%) – HPG (Consensus: 95%) – LS (Consensus: 88%) • Men with PCA with two or more close blood relatives on the same side of the family with a cancer in the following syndromes (broader FH) should be considered for genetic counseling and testing –Postconsensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require further data, and age at diagnosis is important to inquire in the genetic counseling session with patients. – HBOC (Consensus: 93%) – HPC (Consensus: 86%) – LS (Consensus: 86%) • All men with mCRPC should consider genetic testing (Consensus: 67%). –Postconsensus discussion also included consideration of testing men with metastatic, hormone-sensitive PCA to identify germline mutations to inform potential future treatment options and cascade testing in families. • Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal and family history (Consensus 77%).	• Consideration of features of familial and hereditary PCA • Consideration of cancers in HBOC/LS spectrum • Consideration of tumor sequencing results for referral • FH information can be limited; therefore, criteria eliminated need to have Gleason information in relatives. • Lowered threshold of number of relatives with cancers to consider genetic testing • Considered mCRPC†

(continued on following page)

Table 2. Gaps in Genetic Evaluation of Inherited PCA Addressed by Consensus Criteria (continued)

Question	Current NCCN Guidelines	Consensus Criteria	Gaps Addressed by Consensus Criteria
Which genes should be tested based on clinical and/or familial scenarios?	NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian (2.2017) • Personal history of PCA (Gleason ≥ 7) at any age with one or more close blood relatives with ovarian carcinoma at any age or breast cancer ≤ 50 years or two relatives with breast, pancreatic, or PCA (Gleason ≥ 7) at any age • *BRCA1/2* mutation detected by tumor profiling in the absence of germline mutation analysis	• The following genes should be tested in males with PCA meeting criteria for the corresponding syndrome: –*HOXB13* (Syndrome: HPC) (Consensus: 95%) –*BRCA1/BRCA2* (Syndrome: HBOC) (Consensus: 97%) –DNA MMR genes (Syndrome: LS) (Consensus: 73%) • The following genes may be tested in men with PCA with two or more close blood relatives on the same side of the family with a cancer in the following hereditary cancer syndrome spectra (broader FH): –Postconsensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require further data, and age at diagnosis is important to inquire in the genetic counseling session with patients. –*BRCA1/BRCA2* (HBOC cancer spectrum: breast, ovarian, pancreatic, prostate cancers, and melanoma) (Consensus: 98%) –DNA MMR genes (LS cancer spectrum: colorectal, endometrial, upper GI tract, ovarian, pancreatic, prostate, and upper urinary tract cancers, along with sebaceous adenocarcinomas) (Consensus: 97%). –Postconsensus discussion included the moderate nature of evidence of DNA MMR genes and PCA risk, with suggestions to institute IHC testing of prostate tumors for LS to select men with greater chance of carrying a germline DNA MMR mutation. • Men with prostate tumor sequencing showing mutations in the following cancer-risk genes should have confirmatory germline genetic testing for PCA predisposition: *BRCA1/BRCA2* (Consensus:89%), DNA MMR genes (Consensus: 88%), *HOXB13* (68%), *ATM* (61%) • If men with mCRPC undergo genetic testing for treatment determination, the following genes should be tested: *BRCA1/2* (Consensus: 88%), *ATM* (Consensus: 62%)	• Considered testing for genes beyond *BRCA1/2* • Considered confirmatory germline testing for tumor sequencing results revealing mutations in PCA risk genes beyond *BRCA1/2* • Addressed genetic testing for mCRPC†

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Table 2. Gaps in Genetic Evaluation of Inherited PCA Addressed by Consensus Criteria (continued)

Question	Current NCCN Guidelines	Consensus Criteria	Gaps Addressed by Consensus Criteria
How should genetic test results inform prostate career screening?	NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian (2.2017) • Starting at age 45 years for male *BRCA* mutation carriers: – Recommend PCA screening for *BRCA2* carriers – Consider PCA screening for *BRCA1* carriers NCCN Prostate Cancer Early Detection Panel (2.2016) • Insufficient data to support a change in PSA screening and biopsy recommendations for men with germline *BRCA1/2* mutations. • Information about *BRCA1/2* mutation status should be used as part of the discussion about PCA screening.	• *BRCA2* mutation status should be factored into PCA screening discussions (Consensus: 80%). – Screening strategy: ▪ Baseline PSA at age 40 years or 10 years prior to youngest PCA diagnosed in family (Consensus: 56%) ▪ Interval of screening yearly or determined by baseline PSA (Consensus:76%) • *HOXB13* mutation status should be factored into PCA screening discussions (Consensus: 53%). – Screening strategy: ▪ Baseline PSA at age 40 years or 10 years prior to youngest PCA diagnosed in family (Consensus: 52%) ▪ Interval of screening yearly or determined by baseline PSA (Consensus:75%) • For unaffected males at high risk for PCA based on FH of cancer or suspicion for hereditary cancer syndrome who test negative for mutations, PCA screening should follow NCCN PCA Early Detection Guidelines (Consensus: 84%)	• Expanded consideration of *HOXB13* status in PCA screening. • Proposed baseline PSA that factors in age at diagnosis of PCA in the family • Proposed interval of PSA screening
Should genetic test results inform management of early- stage/localized PCA, advanced/high-risk PCA, or mCRPC?	Not addressed	• Of all genes on PCA multigene panels, the following should be factored into management discussion of early- stage/localized PCA: *BRCA2* (Consensus: 64%) • Of all genes on PCA multigene panels, the following should be factored into management discussion of high- risk/advanced PCA: *BRCA2* (Consensus: 97%), *ATM* (Consensus: 59%) • The following genes should be factored into discussions of treatment of mCRPC: *BRCA1* (Consensus: 83%), *BRCA2* (Consensus: 88%), *ATM* (Consensus: 56%)	• Genetic testing to inform management discussions in localized PCA and advanced PCA. • Genetic testing for treatment decisions in mCRPC†

Abbreviations: FDR, first-degree relative; FH, family history; HBOC, hereditary breast and ovarian cancer; HPC, hereditary PCA; IHC, immunohistochemistry; LS, Lynch syndrome; mCRPC, metastatic, castration-resistant PCA; MMR, mismatch repair; NCCN, National Comprehensive Cancer Network; PCA, prostate cancer; PSA, prostate-specific antigen.

*Suggested genetic counseling referral criteria: Male with PCA with any one of the following: having an FDR diagnosed with PCA at age ≤ 55 years; a personal diagnosis of PCA at age ≤ 55 years and an FDR diagnosed with PCA at any age; having an FDR who died as a result of PCA at age younger than 60 years; having family history suggestive of HBOC, HPC, or LS; tumor sequencing showing mutations in hereditary cancer genes; metastatic, castration-resistant PCA. Unaffected males may be referred for genetic counseling on the basis of family history criteria above.

†NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian now includes metastatic PCA in *BRCA1 and 2* testing criteria.

Consensus Model and Evidence Review

An expert opinion consensus model was used to address gaps in evidence-based guidelines for multigene testing for PCA. A modified Delphi model was followed, which incorporated elements of the Delphi process and prior expert opinion consensus conferences relevant to cancer risk and screening (Appendix Fig A1, online only).[43,44] Literature was provided to panel members ahead of the meeting, with initial presentations focused on evidence review by experts. Grade of evidence was summarized as follows, with grade designations adapted from prior literature and consensus models[44,45]: (A) High-grade evidence: at least one prospectively-designed study, or three or more large validation studies, or three or more descriptive studies; (B) Moderate-grade evidence: two cohort or case-control studies; (C) Emerging data: increasing data in support of association to PCA but not yet moderate-grade evidence; (D) Low/Insufficient: limited data or not studied in the context of PCA (Table 1; Appendix Tables A2-A6, online only).

Development of Genetic Evaluation Framework

A conceptual framework was developed to address elements of genetic evaluation, including genetic counseling and genetic testing criteria, genes to test, and screening/management (Fig 1). FH criteria for genetic testing focused on established hereditary cancer syndromes in which PCA has been implicated, as well as broader FH to account for limitations in obtaining detailed FH information.[46,47] Genetic testing consensus discussions focused on genes currently included on commercially available multigene panels (Table 1).

A series of questions were posed to address the genetic evaluation framework (Fig 1). The following overarching questions were addressed:

(1) Which men should undergo genetic counseling and genetic testing for PCA (Fig 1A)? Principles and elements of genetic counseling were presented to panelists, including discussion of cancer genetics, benefits and limitations of genetic testing, financial considerations, implications for the patients and families, and genetic discrimination laws.[39,40] Ethical considerations of genetic testing and the need to clarify patient preferences were also reviewed.[48,49] Genetic testing criteria were based on various personal cancer and FH features. FH considerations included meeting established criteria for HBOC/LS/HPC. Furthermore, considering limitations of obtaining accurate FH information,[46,47] these criteria included FH where at least two close blood relatives have cancers in the HBOC/LS/HPC spectrum as per the NCCN model.[35,36] Finally, metastatic PCA and tumor sequencing were specifically addressed.[31,32] This consensus statement also developed suggested genetic counseling referral criteria following the NCCN model[35,36] (Table 2).

(2) Which genes should be tested based on clinical and/or familial scenarios (Fig 1B)? These questions focused on genes present on current PCA multigene panels (Table 1; Appendix Tables A2-A6). Considerations regarding personal history of PCA included Gleason score, stage, and tumor sequencing results. FH considerations included meeting established criteria for HBOC/LS/HPC or having at least two close blood relatives with cancers in the HBOC/LS/HPC spectrum to address FH limitations. Tumor sequencing results were also considered.

(3) How should genetic test results inform PCA screening (Fig 1C)? This set of criteria focused on genes that inform PCA risk and may be considered in PCA screening discussions. Risk for PCA was reviewed as well as association to aggressive PCA (Appendix Tables A2-A6). Baseline age to check prostate-specific antigen (PSA) and interval to screen based on genetic test results were adapted from other NCCN guidelines.[35,37] PCA screening guidelines by various professional organizations were also reviewed.[37,50-53] Finally, ongoing PCA screening studies incorporating genetic status were summarized.[54]

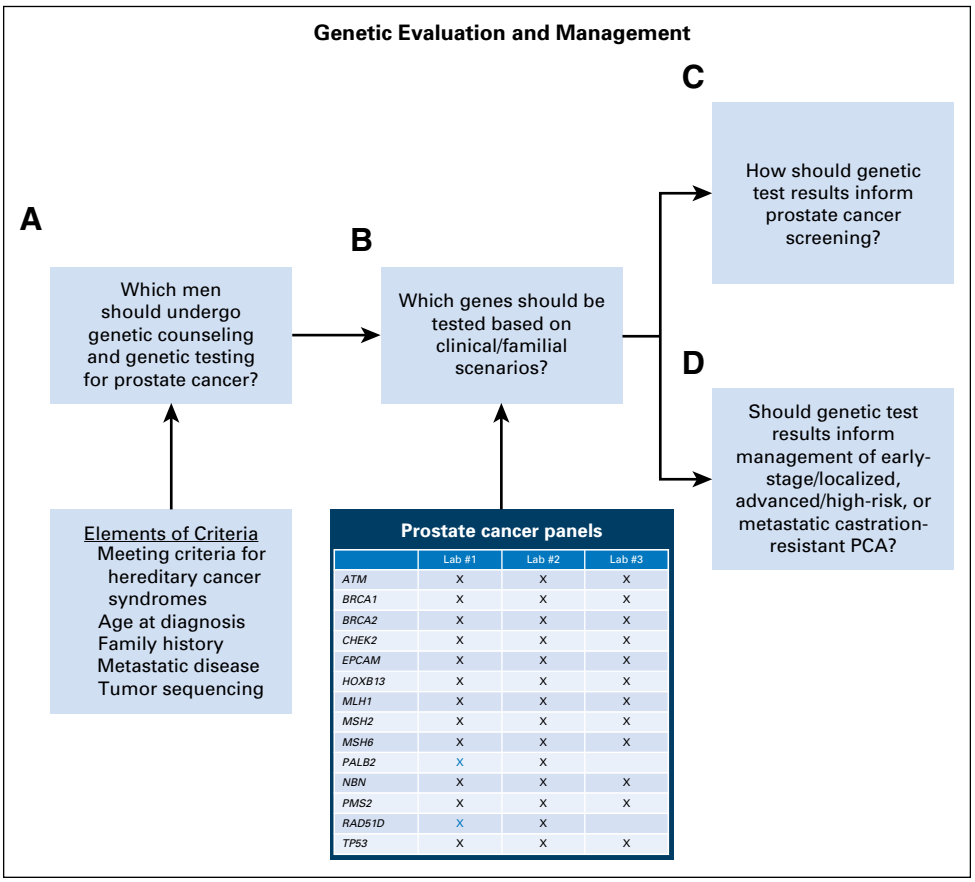

Fig 1. Framework for genetic evaluation of inherited prostate cancer (PCA).

(4) Should genetic test results inform management of early-stage/localized, advanced/high-risk, or metastatic, castration-resistant PCA (mCRPC; Fig 1D)? These questions overall focused on genes on current PCA multigene panels (Table 1) and if they should be factored into management discussions with patients in the setting of early-stage/localized disease, advanced/high-risk disease, or mCRPC. Evidence for PCA aggressiveness was of primary consideration, which was high grade for *BRCA2*, emerging for *ATM*, and limited for other genes on multigene panels (Appendix Tables A2-A6). Genetically informed treatments, such as PARP inhibition and immune checkpoint inhibition, were also considered.[33,34,42]

Strength of Consensus

Votes were cast anonymously using an electronic audience response system. Postconsensus refinement process included readministering select questions where there was debate among panelists. Strength of expert opinion consensus was determined by percentage of agreement with an answer choice: ≥ 75% for strong consensus, 50% to 74% for moderate consensus, and < 50% for lack of consensus. Table 2 provides a comparison of current NCCN guidelines to consensus criteria and identifies the gaps in practice addressed by this consensus statement.

RESULTS

Evidence Review

Various studies were considered in review of evidence for specific genes on multigene panels and PCA risk, including tumor sequencing studies (Table 1; Appendix Tables A2-A6). Current evidence linking *BRCA1* and *BRCA2* mutations to PCA risk was considered high grade, with stronger association for *BRCA2*. Furthermore, *BRCA2* mutations are associated with poor PCA-specific outcomes as well as poorer survival. Evidence linking *HOXB13* mutations to PCA was considered high grade. Evidence of DNA MMR gene mutations to PCA risk was considered moderate grade. Data regarding *ATM* and *NBN* mutations and PCA risk are emerging in favor of association to PCA but are not yet at the level of moderate grade at this time. Other genes on panels have low/insufficient data for PCA risk (Appendix Tables A2-A6).

Consensus Responses

Responses are summarized by overarching questions addressing the genetic evaluation framework, focused on criteria that garnered strong to moderate consensus supported by high- to moderate-grade evidence (Table 2; Appendix Tables A2-A6). Additional considerations are provided to add context to the various criteria, to provide more details regarding discussion that did not make the cutoff for consensus, and to add considerations raised by panel members regarding need for additional discussion or research.

(1) Which men should undergo genetic counseling and genetic testing for prostate cancer (Fig 1A)?

Criteria. Men meeting any one of the following suggested criteria should undergo genetic counseling and genetic testing:

- All men with PCA from families meeting established testing or syndromic criteria for the following:
  - HBOC (Consensus: 93%)
  - HPC (Consensus: 95%)
  - LS (Consensus: 88%)
- Men with PCA with two or more close blood relatives on the same side of the family with a cancer in the following syndromes (broader FH):
  - Postconsensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require additional data, and age at diagnosis is important to inquire in the genetic counseling session with patients.
    - HBOC (Consensus: 93%)
    - HPC (Consensus: 86%)
    - LS (Consensus: 86%)
- All men with mCRPC should consider genetic testing (Consensus: 67%). Postconsensus discussion also included consideration of testing men with metastatic, hormone-sensitive PCA to identify germline mutations to inform potential future treatment options and cascade testing in families.
- Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal history and FH (Consensus: 77%).

Additional considerations. The consensus panel had strong agreement that patients should engage in shared decision making for genetic testing for PCA (Consensus: 77%). Suggested criteria to refer men for genetic counseling included young age at PCA diagnosis (≤ 55 years) in the patient or a first-degree relative, death as a result of PCA in a first-degree relative younger than 60 years, or having FH suggestive of HBOC, HPC, or LS (Table 2). Additional suggested referral criteria include tumor sequencing showing mutations in hereditary cancer genes or metastatic disease (Table 2). The panel achieved strong consensus that African American males should follow the same criteria as males of other race groups until additional genetic data in African American males are available (Consensus: 75%). For males unaffected with PCA and no affected male relatives to test, FH criteria similar to men with PCA would apply.

(2) Which genes should be tested based on clinical and/or familial scenarios (Fig 1B)?

Criteria. Criteria with highest consensus are as follows:

- The following genes should be tested in males with PCA meeting criteria for the corresponding syndrome:
  - *HOXB13* (Syndrome: HPC) (Consensus: 95%)
  - *BRCA1/BRCA2* (Syndrome: HBOC) (Consensus: 97%)
  - DNA MMR genes (Syndrome: LS) (Consensus: 73%)
- The following genes may be tested in men with PCA with two or more close blood relatives on the same side of the family with a cancer in the following hereditary cancer syndrome spectra (broader FH):
  - Postconsensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require further data, and age at diagnosis is important to inquire in the genetic counseling session with patients.
    - *BRCA1/BRCA2* (HBOC cancer spectrum: breast, ovarian, pancreatic, prostate cancers and melanoma) (Consensus: 98%)
    - DNA MMR genes (LS cancer spectrum: colorectal, endometrial, upper GI tract, ovarian, pancreatic, and upper

urinary tract cancers along with sebaceous adenocarcinomas) (Consensus: 97%). Postconsensus discussion included the moderate nature of evidence of DNA MMR genes and PCA risk, with suggestions to institute immunohistochemistry testing of prostate tumors for LS to select men with greater chance of carrying a germline DNA MMR mutation.

- Men with prostate tumor sequencing showing mutations in the following cancer-risk genes should have confirmatory germline genetic testing for PCA predisposition: *BRCA1/BRCA2* (Consensus: 89%), DNA MMR genes (Consensus: 88%), *HOXB13* (68%), *ATM* (61%).
- If men with mCRPC undergo genetic testing for treatment determination, the following genes should be tested: *BRCA1/2* (Consensus: 88%), *ATM* (Consensus: 62%).

(3) How should genetic test results inform PCA screening (Fig 1C)?

Criteria. Criteria with highest consensus are as follows:

- *BRCA2* mutation status should be factored into PCA screening discussions (Consensus: 80%).
  - Screening strategy:
    - Baseline PSA at age 40 years or 10 years prior to youngest PCA diagnosed in family (Consensus: 56%)
    - Interval of screening yearly or determined by baseline PSA (Consensus: 76%)
- *HOXB13* mutation status should be factored into PCA screening discussions (Consensus: 53%).
  - Screening strategy:
    - Baseline PSA at age 40 years or 10 years prior to youngest PCA diagnosed in family (Consensus: 52%)
    - Interval of screening yearly or determined by baseline PSA (Consensus: 75%)

Additional considerations. Postconsensus opinion was to consider a lower age limit to begin PSA screening, perhaps no younger than 35 years. There was strong agreement to perform PSA testing yearly or as dictated by the baseline PSA. This consensus aligns with NCCN Breast and Ovarian guidelines[35] but also expands on the guideline to factor in age at diagnosis of an affected male with PCA in the family for screening initiation as is modeled in colorectal cancer guidelines.[36] *BRCA1* mutation status is part of the NCCN Breast and Ovarian guidelines regarding consideration of baseline PSA at age 45 years.[35]

(4) Should genetic test results inform management of early-stage/localized PCA, advanced/high-risk PCA, and mCRPC (Fig 1D)?

Criteria. Criteria with highest consensus are as follows:

- *BRCA2* mutation status should be factored into management discussion of early-stage/localized PCA: (Consensus: 64%).
- *BRCA2* (Consensus: 97%) and *ATM* (Consensus: 59%) mutation status should be factored into management discussion of high-risk/advanced PCA.
- *BRCA1* (Consensus: 83%), *BRCA2* (Consensus: 88%), *ATM* (Consensus: 56%) mutation status should be factored into mCRPC treatment discussions.

DISCUSSION

To our knowledge, the Philadelphia Prostate Cancer Consensus 2017 was the first attempt to garner expert opinion consensus on key areas in the genetic evaluation continuum for inherited PCA. Increasing scientific insights into the genetic predisposition to inherited PCA, growing multigene testing capabilities, and limited guidelines necessitated expert consensus to address genetic counseling and genetic testing, PCA screening, and management. This conference brought together key stakeholders in PCA treatment, genetic counseling, research, and advocacy to consider the evidence and develop a working framework for genetic counseling, genetic testing, and management of inherited PCA in the multigene testing era. Of particular note was the strong urologic representation at this consensus.

The conference addressed critical gaps in guidelines relevant to genetic evaluation for PCA. These gaps include consideration of FH in cancer syndromes relevant to PCA, consideration of metastatic disease in multigene testing, tumor sequencing, and review of genes on multigene panels for application of genetic testing to PCA. Our conference focused on inherited PCA, which complements a recent consensus conference that addressed germline testing for advanced PCA as part of the overall proceedings.[55] There was agreement in our consensus conference that men with FH meeting strict criteria for HBOC, HPC, or LS and men having FH of cancers in the spectrum of these cancer syndromes while not meeting strict syndromic criteria (broader FH) can be considered for genetic testing. This is an expansion on current NCCN High-Risk Assessment: Breast and Ovarian guidelines,[35] reflects the growing evidence of genetic contribution to PCA beyond *BRCA1* and *BRCA2*, and takes into account limitations of obtaining detailed FH information that could affect meeting criteria for hereditary cancer syndromes.[46,47]

Genetic counseling for PCA will need focused development. Overall, the genetic counseling model should include shared decision making between provider and patient regarding genetic testing. The discussion should clarify patient values and preferences related to screening, risk assessment, and treatment choice. Counseling elements of genetic education; discussion of benefits, risks, and limitations of genetic testing for patients and families; financial implications; and genetic discrimination laws are also important to discuss. Optimal delivery of pretest genetic counseling to patients in the multigene testing era, particularly for genetic testing for advanced/metastatic cancers for targetable mutations, is an area under development. ASCO policy statement 2015 recognized the need for more research on delivery of pretest counseling, particularly in the settings of multigene testing and tumor sequencing, and emphasized the importance of patients to receive genetic education and clarify patient preferences.[56] Furthermore, PCA germline multigene testing studies will help inform counseling discussions of potential results from genetic testing.[38] A closer working relationship between PCA care providers, primary care providers, and cancer genetics specialists will need to be developed to address treatment and management needs while providing patients with optimal genetic education and counseling. Incorporating a genetic counseling and evaluation process into a multidisciplinary PCA clinic setting is one approach.[57]

The mCRPC setting is a unique area that will likely drive a significant proportion of genetic testing for PCA. With emerging insights into targeted therapy for PCA[33,34] and the promise of immunotherapy in MMR-deficient tumors,[42,58] a greater percentage of patients with mCRPC will likely undergo tumor sequencing to uncover targetable mutations, which can have germline implications. The panel had moderate agreement to test all men with mCRPC, which may be strengthened pending future data of germline mutations and targeted agents in mCRPC. Furthermore, some panelists raised questions on testing all men with metastatic PCA and not limiting testing to the castration-resistance setting. Because most of the current data on germline mutations are in the castration-resistant setting,[31-34] proposed criteria were focused on mCRPC, which may change over time. Postconsensus discussion also included the potential for broader scope of genetic testing criteria in the treatment setting versus the risk-assessment setting, which can be considered in future consensus updates. Greater information from this population regarding FH, age at diagnosis, and germline mutation spectrum will be crucial to advance and refine the understanding of genetic predisposition to lethal PCA.

Cost effectiveness of genetic testing for inherited PCA is an important consideration. Our consensus statement outlines targeted testing for selected individuals (in contrast to population-based screening) and is consistent with strategies for hereditary breast cancer testing of *BRCA1/2*. Research has shown that such targeted hereditary testing for a prevalent disease like breast cancer is cost effective under several different economic scenarios when directed at those at highest risk of carrying a mutation.[59-62] For PCA, there is a need to build on the findings of these studies and model survival and quality-adjusted life-years for patients who are at high risk versus those at population risk for PCA. Thus, as we define who should undergo genetic counseling and testing for inherited PCA, we also call for renewed emphasis on the economic evaluation of different strategies to promote patient-centric, high-value genetic evaluation and cancer care.

There are some limitations to consider. Grading of evidence was based on prior consensus conferences, with a noted need for a greater evidence base to inform future criteria development. Our objective was to address the application of multigene testing for PCA through consensus review of existing literature and develop a genetic evaluation framework that can be modified in the future. Another consideration is that the panel consisted of experts and stakeholders engaged in PCA genetics, research, treatment, and advocacy, which may have affected agreement due to breadth of expertise. However, a strength of the consensus was the broad input from thought leaders in various disciplines engaged with PCA, which provided balanced views toward criteria development. The consensus highlighted key areas in need of research, including developing a working definition of HPC in a clinical setting, expanding insights into genetic contribution to aggressive/lethal PCA, developing genetic counseling and referral strategies that engage urologists and primary care providers, addressing the urgent need for focused studies of genetic testing for African American males, evaluating clinical use of genetic testing in PCA screening and management, and expanding health services research for optimized delivery of genetic education to broader populations.

Overall, this consensus conference was a first step to understand the issues confronting application of genetic testing to PCA and develop a meaningful framework using the best evidence available. The need to revise and optimize consensus criteria is noted, based on the dynamic nature of knowledge and progress in this field. Several consensus panel members are also members of NCCN guidelines panels, which may lead to consideration of consensus review and criteria for incorporation into respective NCCN guidelines regarding genetic testing for inherited PCA. NCCN Prostate Cancer Early Detection guidelines will likely include stronger consideration of *BRCA* mutation status in PCA screening discussions and may consider this consensus statement in future guideline updates.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Janssen Pharmaceuticals, Astellas/Medivation/Pfizer, Bayer Pharmaceuticals, Ferring Pharmaceuticals, MDxHealth, Myriad Genetics, Roche Diagnostics, Ambry Genetics, GenomeDX, Genomic Health, Invitae, OncLive, and American HIFU.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017

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

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Patents, Royalties, Other Intellectual Property: OHMX

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Patents, Royalties, Other Intellectual Property: Method for predicting the risk of prostate cancer morbidity and mortality, predicting and treating prostate cancer, methods for predicting likelihood of responding to treatment, chromosome copy number gain as a biomarker of urothelial carcinoma lethality, drug combinations to treat cancer, somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma (patent), Up-to-Date royalties, Wolters Kluwer royalties
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Consulting or Advisory Role: AbbVie, Bayer, Theralogix, Tolmar, Blue Earth Diagnostics
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Patents, Royalties, Other Intellectual Property: I am a coauthor on a patent issued to the University of Michigan on ETS gene fusions in prostate cancer. The diagnostic field of use has been licensed to Hologic/Gen-Probe, who has sublicensed some rights to Ventana Medical Systems/Roche.
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Acknowledgment

We thank the Foundation for Breast and Prostate Health for collaborating with the Sidney Kimmel Cancer Center at Jefferson on this consensus effort. We also thank our patient advocates and their family members who contributed their time and personal experiences to this consensus conference: John Buehler, Robin Cole, and Peter Kaye, Sr.

Appendix

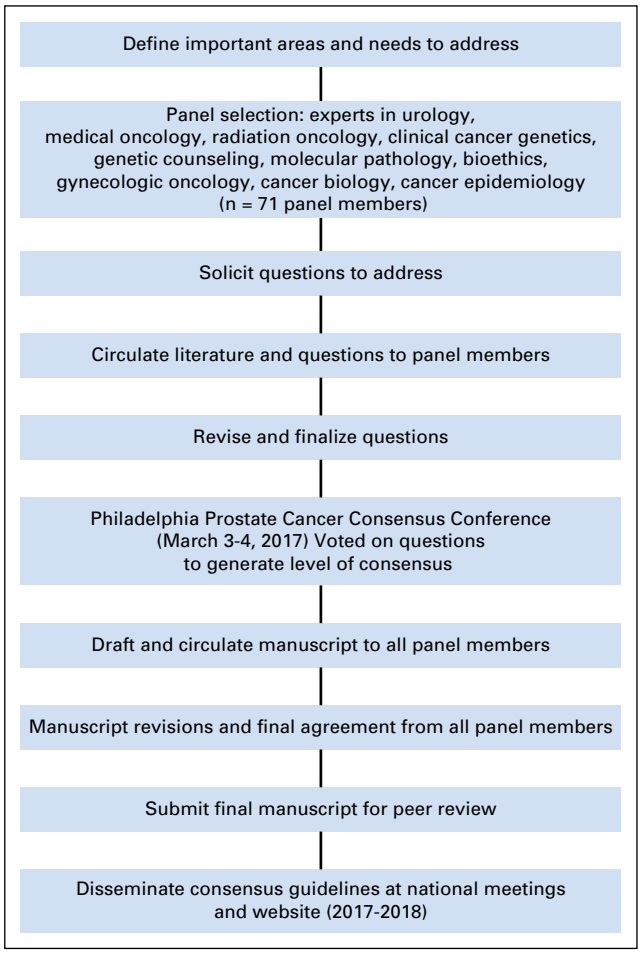

Fig A1. Overall consensus model.

Table A1. Consensus Conference Panel Members

Panel Member	Institution	Specialty
Wassim Abida, MD, PhD	Memorial Sloan Kettering Cancer Center	Medical Oncology
Chris H. Bangma, MD, PhD	Erasmus Medical Center, Rotterdam, the Netherlands	Urology
Mitchell C. Benson, MD	Columbia University	Urology
Amie Blanco, MS, LCGC	UCSF Helen Diller Family Comprehensive Cancer Center	Genetic Counseling
John Buehler	N/A	Patient Advocate
Arthur "Bud" Burnett, MD, MBA	Johns Hopkins Medical Institutions	Urology
William J. Catalona, MD	Northwestern University, Feinberg School of Medicine; R.H. Lurie Comprehensive Cancer Center	Urology
Robin Cole	N/A	Patient Advocate
Kathleen A. Cooney, MD	University of Utah School of Medicine	Medical Oncology/Genetics
Matthew Cooperberg, MD, MPH	UCSF Helen Diller Family Comprehensive Cancer Center	Urology
E. David Crawford, MD	University of Colorado, Denver	Urology
Robert B. Den, MD	Jefferson Sidney Kimmel Cancer Center	Radiation Oncology
Adam P. Dicker, MD, PhD	Jefferson Sidney Kimmel Cancer Center	Radiation Oncology
Scott Eggener, MD	University of Chicago	Urology
Neil Fleshner, MD	University of Toronto, Princess Margaret Cancer Centre	Urology
Matthew L. Freedman, MD	Harvard Medical School/Dana-Farber Cancer Institute	Medical Oncology/Genetics
Veda N. Giri, MD	Jefferson Sidney Kimmel Cancer Center	Medical Oncology/Clinical Cancer Genetics
Leonard G. Gomella, MD	Jefferson Sidney Kimmel Cancer Center	Urology
Freddie C. Hamdy, FRCS, FMedSci	University of Oxford, Oxford England	Urology
Jean Hoffman-Censits, MD	Jefferson Sidney Kimmel Cancer Center	Medical Oncology
Mark D. Hurwitz, MD	Jefferson Sidney Kimmel Cancer Center	Radiation Oncology
Colette Hyatt, MS, LCGC	Jefferson Sidney Kimmel Cancer Center	Genetic Counseling
William B. Isaacs, PhD	Johns Hopkins Medical Institutions	Genetics Research
Christopher J. Kane, MD	University of California San Diego	Urology
Philip Kantoff, MD	Memorial Sloan Kettering Cancer Center	Medical Oncology
R. Jeffrey Karnes, MD	Mayo Clinic, Rochester	Urology
Lawrence I. Karsh, MD	The Urology Center of Colorado	Urology
Peter Kaye, Sr	N/A	Patient Advocate
Wm. Kevin Kelly, DO	Jefferson Sidney Kimmel Cancer Center	Medical Oncology
Eric A. Klein, MD	Cleveland Clinic	Urology
Karen E. Knudsen, PhD	Jefferson Sidney Kimmel Cancer Center	Oncology Research
Daniel W. Lin, MD	University of Washington	Urology
Kevin R. Loughlin, MD, MBA	Brigham and Women's Hospital, Harvard Medical School	Urology
Grace Lu-Yao, PhD	Jefferson Sidney Kimmel Cancer Center	Population Science
S. Bruce Malkowicz, MD	University of Pennsylvania	Urology
Mark J. Mann, MD	Jefferson Sidney Kimmel Cancer Center	Urology
J. Ryan Mark, MD	Jefferson Sidney Kimmel Cancer Center	Urology
Peter A. McCue, MD	Jefferson Sidney Kimmel Cancer Center	Pathology
Martin M. Miner, MD	Brown University	Primary Care
Todd Morgan, MD	University of Michigan	Urology
Judd W. Moul, MD	Duke University, Duke Cancer Institute	Urology
Ronald E. Myers, PhD	Jefferson Sidney Kimmel Cancer Center	Medical Decision Making Research/Population Science
Sarah M. Nielsen, MS, CGC	The University of Chicago	Genetic Counseling
Elias Obeid, MD, MPH	Fox Chase Cancer Center	Medical Oncology/Genetics
Christian P. Pavlovich, MD	Johns Hopkins Medical Institutions	Urology
Stephen C. Peiper, MD	Jefferson Sidney Kimmel Cancer Center	Pathology
David F. Penson, MD, MPH	Vanderbilt University Medical Center	Urology
Daniel Petrylak, MD	Yale University	Medical Oncology
Curtis A. Pettaway, MD	The University of Texas MD Anderson Cancer Center	Urology
Robert Pilarski, MS, LGC, MSW	The Ohio State University	Genetic Counseling
Peter A. Pinto, MD	National Cancer Institute	Urology
Wendy Poage, MHA	Prostate Conditions Education Council	Prostate Cancer Education/Advocacy
Ganesh V. Raj, MD, PhD	University of Texas Southwestern Medical Center at Dallas	Urology
Timothy R. Rebbeck, PhD	Dana Farber Cancer Institute and Harvard TH Chan School of Public Health	Genetics Research
Mark E. Robson, MD	Memorial Sloan Kettering Cancer Center	Breast Oncology/Genetics
Matt T. Rosenberg, MD	Mid-Michigan Health Center	Primary Care
Howard Sandler, MD, MS	Cedars-Sinai Medical Center	Radiation Oncology
Oliver Sartor, MD	Tulane University Medical School	Medical Oncology
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Gordon F. Schwartz, MD	Foundation for Breast and Prostate Health	Breast Surgery

(continued on following page)

Table A1. Consensus Conference Panel Members (continued)

Panel Member	Institution	Specialty
Mark S. Shahin, MD	Hanjani Institute for Gynecologic Oncology; Abington Hospital-Jefferson Health	Gynecologic Oncology
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Brian Shuch, MD	Yale University	Urology
Howard R. Soule, PhD	Prostate Cancer Foundation	Basic and Clinical Research
Scott A. Tomlins, MD, PhD	University of Michigan Medical School	Pathology
Edouard J. Trabulsi, MD	Jefferson Sidney Kimmel Cancer Center	Urology
Robert Uzzo, MD	Fox Chase Cancer Center	Urology
Donald J. Vander Griend, PhD	The University of Chicago	Basic and Clinical Research
Patrick C. Walsh, MD	Johns Hopkins Medical Institutions	Urology
Carol J. Weil, JD	National Cancer Institute	Bioethics
Richard Wender, MD	American Cancer Society	Family and Community Medicine

NOTE. Additional manuscript contributors: Gerald L. Andriole, MD (Washington University School of Medicine; Urology); Justin E. Bekelman, MD (University of Pennsylvania Perelman School of Medicine; Radiation Oncology and Medical Ethics and Health Policy).

The following series of tables highlight the studies referenced by the consensus panel concerning grade of evidence for prostate cancer (PCA) risk by genes on PCA multigene panels. Grade of evidence is provided in the titles of Tables A2-A6. (A) High-grade evidence: At least one prospectively designed study or three or more large validation studies or three or more descriptive studies; (B) Moderate-grade evidence: two cohort or case-control studies; (C) Emerging data: increasing data in support of association to PCA, but not yet moderate-grade evidence; (D) Low/insufficient: limited data or not studied in the context of PCA.

Table A2. Case Series of *BRCA1* and *BRCA2* and PCA Risk [*BRCA1* and *BRCA2* (Evidence: A)]

First Author	Population	PCA Risk (*BRCA1*)	PCA Risk (*BRCA2*)	Comments
BCLC[1]	BCLC included 173 *BRCA2*-linked or mutation-positive families (3,728 individuals and 333 cancers*)	Not assessed	Overall: RR, 4.65 (95% CI, 3.48 to 6.22)	Men younger than 65 years: RR, 7.33; 95% CI, 4.66 to 11.52
Thompson[2]	BCLC family set that included 7,106 women and 4,741 men, among whom 2,245 were carriers of *BRCA1* mutations, 1,106 were tested noncarriers, and 8,496 were not tested	Overall: RR, 1.07 (95% CI, 0.75 to 1.54)	Not assessed	Men younger than 65 years: RR, 1.82; 95% CI, 1.01 to 3.29
Mersch[3]	Clinical genetics population at a single institution from 1997-2013. Compared cancer incidence to US Statistics Report by CDC for general population cancer incidence	SIR, 3.809 (95% CI, 0.766 to 11.13)	SIR, 4.89 (95% CI, 1.959 to 10.075)	
Agalliu[4]	290 men (white, n = 257; African American, n = 33) diagnosed with PCA at younger than 55 years and unselected for family history	Not assessed	RR, 7.8 (95% CI, 1.8 to 9.4)	
Kote-Jarai[5]	1,832 men diagnosed with PCA between age 36 and 88 years who participated in the UK Genetic Prostate Cancer Study	Not assessed	RR, 8.6 (95% CI, 5.1 to 12.6)	MLPA was not used; therefore, the mutation frequency may be an underestimate, given the inability to detect large genomic rearrangements.
Leongamornlert[6]	913 men with PCA who participated in the UK Genetic Prostate Cancer Study; included 821 cases diagnosed between age 36 and 65 years, regardless of family history, and 92 cases diagnosed at older than 65 years with a family history of PCA	RR, 3.75 (95% CI, 1.02 to 9.6)	Not assessed	

NOTE. Adapted from the National Cancer Institute PDQ Genetics of Prostate Cancer Summary.[7]
Abbreviations: BCLC, Breast Cancer Linkage Consortium; CDC, Centers for Disease Control and Prevention; MLPA, multiplex ligation-dependent probe amplification; PCA, prostate cancer; RR, relative risk; SIR, standardized incidence ratio.
*Includes all cancers except breast, ovarian, and nonmelanoma skin cancers.

Table A3. Case-Control Studies of *BRCA1* and *BRCA2* and Survival Outcomes (Evidence: A for *BRCA2*)

First Author	Cases	Controls	PCA-Specific Survival	Overall Survival	Comments
Tryggvadóttir[8]	30 men diagnosed with PCA who were carriers of *BRCA2* 999del5 founder mutation (Icelandic population)	59 men with PCA matched by birth and diagnosis year and confirmed not to carry the *BRCA2* 999del5 mutation	*BRCA2* 999del5 mutation was associated with a higher risk of death from PCA (HR, 3.42; 95% CI, 2.12 to 5.51), which remained after adjustment for tumor stage and grade (HR, 2.35; 95% CI, 1.08 to 5.11).	Not assessed	
Edwards[9]	21 men diagnosed with PCA who harbored a *BRCA2* mutation: six with early-onset disease (≤ 55 years) from a United Kingdom PCA study and 15 unselected for age at diagnosis from a United Kingdom clinical series	1,587 age- and stage-matched men with PCA	Not assessed	Overall survival was lower in carriers of *BRCA2* mutations (4.8 years) than in noncarriers (8.5 years); HR, 2.14 (95% CI, 1.28 to 3.56; $P = .003$).	
Gallagher[10]	832 AJ men diagnosed with localized PCA between 1988 and 2007, of whom there were six carriers of *BRCA1* mutations and 20 carriers of *BRCA2* mutations	454 AJ men with no history of cancer	After adjusting for stage, PSA, Gleason score, and therapy received: – Carriers of *BRCA1* 185delAG mutation had a greater risk of death as a result of PCA (HR, 5.16; 95% CI, 1.09 to 24.53; $P = .001$). –Carriers of *BRCA2* 6174delT mutation had a greater risk of death as a result of PCA (HR, 5.48; 95% CI, 2.03 to 14.79; $P = .001$).	Not assessed	The *BRCA1* 5382insC founder pathogenic variant was not tested in this series.
Thorne[11]	40 men diagnosed with PCA who were carriers of *BRCA2* mutations from 30 familial breast cancer families from Australia and New Zealand	97 men from 89 familial breast cancer families from Australia and New Zealand with PCA and no *BRCA* mutation found in the family	*BRCA2* carriers had increased risk of PCA-specific mortality (HR, 4.5; 95% CI, 2.12 to 9.52; $P <$ .001), compared with noncarrier	*BRCA2* had increased risk of death (HR, 3.12; 95% CI, 1.64 to 6.14; $P <$ .001), compared with noncarriers	There were too few *BRCA1* carriers available to include in the analysis.
Castro[12]	2,019 men diagnosed with PCA from the United Kingdom, of whom 18 were carriers of *BRCA1* mutations and 61 were carriers of *BRCA2* mutations	1,940 men who were *BRCA1/2* noncarriers	PCA-specific survival at 5 years: – *BRCA1*: 80.8% (95% CI, 56.9% to 100%) – *BRCA2*: 67.9% (95% CI ,53.4% to 82.4%; $P <$ .001) – Controls: 90.6% (95% CI, 88.8% to 92.4%; $P <$ .001)	Overall survival at 5 years: – *BRCA1*: 82.5% (95% CI, 60.4% to 100%) – *BRCA2*: 57.9% (95% CI, 43.4% to 72.4%; $P <$ .001) – Controls: 86.4% (95% CI, 84.4% to 88.4%; $P <$ .001)	For localized PCA, metastasis-free survival was also higher in controls than in mutation carriers (93% *v* 77%; HR, 2.7).
Castro[13]	1,302 men from the United Kingdom with local or locally advanced PCA, including 67 carriers of *BRCA1/2* mutations	1,235 men who were *BRCA1/2* noncarriers	PCA-specific survival: – *BRCA1/2*: 61% at 10 years – Noncarriers: 85% at 10 years	Not assessed	Multivariate analysis confirmed *BRCA* mutations as an independent prognostic factor for cause-specific survival: (HR, 2.17; 95% CI, 1.16 to 4.07; $P = .016$)

NOTES. Adapted from the National Cancer Institute PDQ Genetics of Prostate Cancer Summary.[7] Rates of *BRCA1/BRCA2* mutations in metastatic PCA described in the paper.
Abbreviations: AJ, Ashkenazi Jewish; HR, hazard ratio; PCA, prostate cancer; PSA, prostate-specific antigen.

Table A4. *HOXB13* (G84E) and Association to PCA Risk (Evidence: A)

First Author	Cases	Controls	OR of PCA Risk
Ewing[14]	94 unrelated patients from hereditary PCA families; four probands carried G84E mutation. Confirmation: 5,083 PCA cases (combination of hereditary, familial, early-onset, or localized PCA cases)	1,401 screened controls	Men with a positive family history of PCA: 2.2% *v* negative: 0.8% (OR, 2.8; 95% CI, 1.6 to 5.1; $P < .001$) Men younger than 55 years at diagnosis: 2.2% *v* older than 55 years: 0.8% (OR, 2.7; 95% CI, 1.6 to 4.7; $P < .001$) Men with a positive family history of PCA and younger than 55 years at diagnosis: 3.1% *v* a negative family history of PCA and age at diagnosis older than 55 years: 0.6% (OR, 5.1; 95% CI, 2.4 to 12.2; $P < .001$) Control subjects: 0.1%-0.2%
Xu[15]	2,443 PCA families from ICPCG. Among carrier families, cases included 382 men with PCA.	2,443 PCA families from ICPCG; among carrier families, controls included 137 men without PCA	OR, 4.42; 95% CI, 2.56 to 7.64
Akbari[16]	1,843 cases with PCA	2,225 control men without PCA	5.8; 95% CI, 1.3 to 26.5; $P = .01$
Breyer[17]	928 familial PCA probands	930 controls without personal or family history of PCA	7.9; 95% CI, 1.8 to 34.5; $P = .0062$; carrier rate was 1.9% among all familial case probands and 2.7% among probands of pedigrees with three or more affected with PCA.
Karlsson[18]	5,003 population-based cases in Sweden (CAPS and Stockholm-1 studies)	4,693 population-based controls in Sweden (CAPS and Stockholm-1 studies)	CAPS: OR, 3.4; 95% CI, 2.2 to 5.4; Stockholm-1: OR, 3.5; 95% CI, 2.4 to 5.2 Young-onset: OR, 8.6; 95% CI, 5.1 to 14.0 Hereditary PCA: OR, 6.6; 95% CI, 3.3 to 12.0
Kluzniak[19]	3,515 patients with PCA in Poland	2,604 controls in Poland	OR, 5.0; 95% CI, 1.5 to 16.7; $P = .008$ Familial PCA: OR, 8.4; 95% CI, 1.9 to 37.7; $P = .005$
Laitinen[20]	4,000 PCA cases in Finland	5,000 controls in Finland	All cases and controls: OR, 7.1; 95% CI, 5.5 to 9.3 Hereditary PCA: OR, 8.8; 95% CI, 4.9 to 15.7
Stott-Miller[21]	1,310 population-based PCA cases from Seattle region	1,259 age-matched controls	Overall: OR, 3.3; 95% CI, 1.21 to 8.96
Gudmundsson[22]	9,988 PCA cases in Iceland, Chicago, Spain, Netherlands, Romania, United Kingdom	61,994 controls in Iceland, Chicago, Spain, Netherlands, Romania, United Kingdom	OR, 7.1; 95% CI, 4.62 to 10.78; $P_{comb} < .001$
Witte[23]	Family-based PCA study (647 cases); aggressive incident PCA (998 cases)	Family-based PCA study (477 controls); aggressiveness study (542 controls)	OR, 4.8; $P = .01$

Abbreviations: CAPS, Cancer of the Prostate in Sweden; ICPCG, International Consortium of Prostate Cancer Genetics; OR: odds ratio; PCA, prostate cancer; *P*_comb, combined *P* value.

Table A5. DNA MMR Genes, PCA Risk, and Molecular Data (Evidence: B)

First Author	Population	Results	Comments
Grindedal[24]	106 male DNA MMR mutation carriers from Norwegian Cancer Registry	Expected number of PCAs was 1.52 compared with nine observed ($P < .01$). Mean age of onset of PCA was 60.4 years compared with 66.6 expected ($P = .006$). No. of men with Gleason score between 8 and 10 was significantly higher than expected ($P < .001$).	Loss of MMR gene expression was found in seven of eight tumors.
Haraldsdottir[25]	Compared rates of PCA from Lynch syndrome families at academic institution to general population rates of PCA in SEER	PCA was observed in 11 of 188 males with Lynch syndrome. SIR, 4.87; 95% CI, 2.43 to 8.71	Impaired MMR expression and microsatellite instability were seen in one out of two PCA specimens available for testing.
Bauer[26]	95 individuals were identified as members of potential Lynch syndrome families from a hereditary PCA study; underwent radical prostatectomy and 35 tumors from 31 families underwent MSI analysis.	Two of 35 prostate tumors were MSI high, suggestive of germline DNA MMR mutation.	One patient had IHC loss that correlated with germline MMR mutation.
Raymond[27]	Two family cancer registries for total of 198 Lynch syndrome families PCA incidence in Lynch syndrome families was compared with SEER data	Cumulative lifetime risk of PCA (to age 80 years) was 30.0% in carriers of MMR gene mutations (95% CI, 16.54 to 41.30; $P = .07$), compared with 17.84% in the general population; HR (to age 80 years) for PCA in carriers of MMR gene mutations in the combined data set was 1.99 (95% CI, 1.31 to 3.03; $P = .0013$). HR, 2.48 (95% CI, 1.34 to 4.59; $P = .0038$) among men age 20 to 59 years	
Ryan[28]	Systematic review and meta-analysis that included 23 studies (six studies with molecular characterization and 18 risk studies, of which 12 studies quantified risk for PCA)	RR of PCA in carriers of MMR gene pathogenic variants was estimated to be 3.67 (95% CI, 2.32 to 6.67).	In the six molecular studies, 73% (95% CI, 57% to 85%) of PCAs in carriers of germline MMR mutations were MMR deficient.
Rosty[29]	32 PCA cases with germline MMR gene mutations from Colon Cancer Family Registry	RR of PCA was highest in carriers of *MSH2* mutations (RR, 5.8; 95% CI, 2.6 to 20.9) RR of PCA in *MLH1* mutation carriers: 1.7; 95% CI, 1.1 to 6.7 RR of PCA in *MSH6* mutation carriers: 1.3; 95% CI, 1.1 to 5.3	Loss of MMR protein expression by IHC was observed in 22 tumors (69%); the pattern of loss of protein expression was 100% concordant with the germline mutation.

Abbreviations: HR, hazard ratio; IHC: immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; PCA, prostate cancer; RR, relative risk; SIR, standardized incidence ratio.

Table A6. Additional Genes on Multigene Panels and Association to PCA

Gene	Grade of Evidence	First Author	Population	Results
CHEK2	D	Cybulski[30]	3,750 Polish men with PCA *v* 3,956 Polish men with no history of cancer	Any *CHEK2* mutation: OR, 1.9; 95% CI, 1.6 to 2.2; $P < .001$ PCA diagnosed younger than 60 years: OR, 2.3; 95% CI, 1.8 to 3.1; $P < .001$ Familial PCA: OR, 2.7; 95% CI, 2.0 to 3.7; $P < .001$
		Pritchard[31]	Metastatic PCA unselected for family history	10 of 534 metastatic PCAs had *CHEK2* germline mutation (1.87%)
ATM	C	Pritchard[31]	Metastatic PCA unselected for family history	11 of 692 (1.6%) metastatic PCAs had *ATM* germline mutation
		Na[32]	313 lethal PCA *v* 486 low-risk/localized PCA	*ATM* + *BRCA1* + *BRCA2* associated with lethal PCA ($P = .0007$) and shorter survival *ATM* alone borderline association to lethal PCA ($P = .06$)
		Mateo[33]	49 men with mCRPC; phase II trial of treatment with olaparib	Three of 49 (6.1%) had germline *ATM* mutations
NBN	C	Cybulski[34]	Poland: Familial PCA = 56 Nonfamilial PCA = 305 Controls = 1,500	*NBN* founder mutation 657del5 presence: Familial PCA: five of 56 (9%; OR, 16; $P < .001$) Nonfamilial PCA: seven of 305 (OR, 3.9; $P = .01$) Controls: nine of 1,500 (0.6%)
		Cybulski[30]	Cases = 3,750, Controls = 3,956	PCA: OR, 2.5; 95% CI, 1.5 to 4.0 Age diagnosis younger than 60 years; OR, 3.1; 95% CI, 1.5 to 6.4 Familial PCA: OR, 4.3; 95% CI, 2.0 to 9.0
		Pritchard[31]	Metastatic PCA unselected for family history	Two of 692 (0.29%) metastatic PCAs had *NBN* germline mutation
PALB2	D	Pritchard[31]	Metastatic PCA unselected for family history	Three of 692 (0.43%) metastatic PCAs had *PALB2* germline mutation
RAD51D	D	Pritchard[31]	Metastatic PCA unselected for family history	Three of 692 (0.43%) metastatic PCAs had *RAD51D* germline mutation
TP53	D	—	—	—

Abbreviations: OR, odds ratio; PCA, prostate cancer.

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