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Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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abstract

PURPOSE Germline testing (GT) is a central feature of prostate cancer (PCA) treatment, management, and hereditary cancer assessment. Critical needs include optimized multigene testing strategies that incorporate evolving genetic data, consistency in GT indications and management, and alternate genetic evaluation models that address the rising demand for genetic services.

METHODS A multidisciplinary consensus conference that included experts, stakeholders, and national organization leaders was convened in response to current practice challenges and to develop a genetic implementation framework. Evidence review informed questions using the modified Delphi model. The final framework included criteria with strong (> 75%) agreement (Recommend) or moderate (50% to 74%) agreement (Consider).

RESULTS Large germline panels and somatic testing were recommended for metastatic PCA. Reflex testing—initial testing of priority genes followed by expanded testing—was suggested for multiple scenarios. Metastatic disease or family history suggestive of hereditary PCA was recommended for GT. Additional family history and pathologic criteria garnered moderate consensus. Priority genes to test for metastatic disease treatment included *BRCA2, BRCA1,* and mismatch repair genes, with broader testing, such as *ATM*, for clinical trial eligibility. *BRCA2* was recommended for active surveillance discussions. Screening starting at age 40 years or 10 years before the youngest PCA diagnosis in a family was recommended for *BRCA2* carriers, with consideration in *HOXB13, BRCA1, ATM*, and mismatch repair carriers. Collaborative (point-of-care) evaluation models between health care and genetic providers was endorsed to address the genetic counseling shortage. The genetic evaluation framework included optimal pretest informed consent, post-test discussion, cascade testing, and technology-based approaches.

CONCLUSION This multidisciplinary, consensus-driven PCA genetic implementation framework provides novel guidance to clinicians and patients tailored to the precision era. Multiple research, education, and policy needs remain of importance.

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INTRODUCTION

The role of germline testing (GT) for prostate cancer (PCA) has increased, with growing precision treatment implications and expanded testing options.[1,2] A primary driver for GT is now precision therapy for metastatic disease where genetic results inform options and strategies for targeted treatment, therapeutic planning, and clinical trials.[1-4] Approximately 12% to 17% of men with metastatic PCA harbor germline mutations, primarily in DNA repair genes, such as

BRCA2, CHEK2, BRCA1, ATM, PALB2, and the DNA mismatch repair (MMR) genes,[5] which are increasingly informing options for poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, platinum chemotherapy, and clinical trials.[1-4,6] In early-stage disease, emerging data suggest that men with germline *BRCA2* mutations, and possibly *ATM* mutations, have higher rates of upgrading of prostate biopsies while on active surveillance (AS).[7] GT results are considered increasingly in PCA early detection discussions, particularly for men with *BRCA2* mutations for which data support higher rates of PCA detection, younger age at diagnosis, and more clinically significant disease.[8-10] Many of the genes that are important for PCA therapy, management, and early detection are associated with hereditary cancer syndromes.[11] Pathogenic variants in *BRCA1* and *BRCA2* are associated with hereditary breast and ovarian cancer (HBOC). DNA MMR genes—*MLH1, MSH2, PMS2, MSH6,* and *EPCAM*—are associated with Lynch syndrome.[11-16] These and other hereditary cancer syndromes confer risks for multiple cancers that must be addressed for men and their kindred.[8,16]

As PCA GT has increased, new practice and implementation challenges have emerged in three major areas: expanded options for multigene panels, with a resultant lack of clarity regarding optimized panel use and priority genes to test; variability in guidelines regarding GT indications and genetically based management that incorporates emerging data; and a shortage of genetic services.[1,17-21] Testing options have expanded rapidly, which include focused, guideline-based, comprehensive, and reflex panels.[17,18] Panels include genes with strong, limited, and unknown risk for PCA and that yet confer risks for multiple cancers.[18] There is a need for clarity on panel choice and priority genes to test in men with metastatic PCA, nonmetastatic PCA, and men at high risk for PCA that balances the benefits of expanded testing (eg, identifying actionable mutations) with considerations (eg, higher rates of variants of uncertain significance [VUS]).[3,8,10]

Uniform guidance is also needed regarding GT indications and genetically based PCA management that incorporates rapidly emerging, sometimes conflicting, data. Current National Comprehensive Cancer Network (NCCN) guidelines have variability regarding GT on the basis of pathologic—stage and Gleason/Grade Group—and family history (FH) criteria.[3,8,9] Management guidance is also needed in multiple areas with consideration of gene-specific outcomes, such as treatment of metastatic disease with variable responses by DNA repair mutations[1-4,6]; AS discussions that consider strong data for *BRCA2*, but limited data for *BRCA1* and *ATM*[7]; and broader consideration of genes for PCA early detection.[1,2,11] In particular, strategies for PCA early detection need clarification regarding age to begin screening on the basis of genetic status.[8,9]

Furthermore, the rising need for PCA GT has created a critical shortage of genetic counseling (GC) services.[1,19] Health care providers, such as oncologists and urologists, increasingly are ordering PCA GT to expedite testing for management.[20,21] Concerns include limited guidance on optimal pretest informed consent, optimal panel testing strategies for comprehensive genetic evaluation, inclusion of personal history and FH, and balancing timely GT with appropriate referral to GC to address patient and family needs.[1,20,21] As referral of all men to GC for PCA GT is not sustainable, health care and genetic providers need implementation strategies that incorporate alternate genetic evaluation models for the timely and responsible delivery of PCA GT for men and their families.[1,19]

The 2019 Philadelphia Prostate Cancer Consensus Conference was convened to address challenges in PCA germline evaluation and implementation with attention to evolving genetic and precision medicine data. This meeting was a follow-up to the 2017 Philadelphia Consensus Conference, which focused on the role of GT for inherited PCA risk.[18] The 2019 conference had the following 3 goals: to define optimal GT strategies that incorporate expansion of panel testing options and evolving genetic data, to propose consistent PCA GT indications and management, and to propose alternate genetic evaluation models to address the GC shortage. An expert, consensus-driven genetic implementation framework was developed for health care and genetic providers to streamline GT for PCA in the precision medicine era.

METHODS

Overarching Questions Addressing Implementation Gaps

The following questions were primary drivers of the conceptual framework:

1. Which men should be considered for germline PCA genetic testing?
2. Which panels should be considered and which genes should be prioritized for testing?
3. What PCA-specific recommendations should be considered on the basis of genetic results?
4. What is optimal informed consent for PCA GT?
5. What collaborative strategies may facilitate PCA genetic evaluation between health care and genetic providers?
6. What post-test disclosure strategies are most appropriate on the basis of genetic results?
7. What barriers must be addressed to enhance PCA GT?

Consensus Conference Participants

The Consensus Conference included 97 participants spanning the fields of urology, medical oncology, radiation oncology, clinical genetics, genetic counseling, primary care, pathology, implementation science, population science, epidemiology, and basic science. Patient stakeholders and advocates were active participants. Members of several national organizations, which included NCCN representatives, also participated. Academic and

community practices were represented, and panelists were from multiple regions of the United States, as well as Europe and Australia. The final voting panel included 76 participants (Table 1).

Consensus Process

The modified Delphi model was followed that incorporated elements of the Delphi process as previously published.[18,22,23] Literature was provided to panel members before the meeting. Multiple expert presentations summarizing evidence relevant to genetic implementation were delivered. Evidence review is summarized in the Data Supplement.

Evidence Review

Thematic topics included: genetic contribution to PCA risk/aggressiveness[24-54]; germline mutations by PCA clinical and molecular characteristics[5,55-66]; PCA clinical multigene testing data[60,61,67]; germline mutations in diverse populations[5,24,30,49,61,68-74]; PCA genetic testing capabilities and considerations[17,75-81] (Fig 1); implementation of GC[1,3,8,9,17,76,82-93]; NCCN PCA genetic testing guidelines and current variability[3,8,9]; GT for PCA precision medicine in the metastatic setting[2,4,6,56,58,94-99]; germline implications for AS of early-stage PCA[7,35,99,100,101]; and germline implications for PCA early detection.[8-10,102] Table 2 provides a summary of genetic data for PCA risk and aggressiveness. Full evidence summary is provided in the Data Supplement.

Strength of Consensus

Votes were cast anonymously using a Web-based polling platform. Strength of consensus was ≥ 75% agreement for strong consensus, 50% to 74% agreement for moderate consensus, and < 50% agreement for lack of consensus.[22,23]

Development of PCA Genetic Evaluation and Management Framework

A conceptual framework for PCA genetic evaluation and management was developed (Fig 2). Criteria that achieved strong consensus were designated as "Recommend" and those with moderate consensus were designated as "Consider" in the final framework.

RESULTS

Key premises

The following are guiding principles for clinical genetic evaluation:

Premises based on prior literature and Consensus Conference expert guidance:

- In-person GC is a gold standard of genetics practice.[2,76,82-84]
- Patients' psychosocial needs or preferences should dictate the mode of counseling.[1,82-84]
- Full FH is important to collect during the genetic evaluation process:[1,82-84]

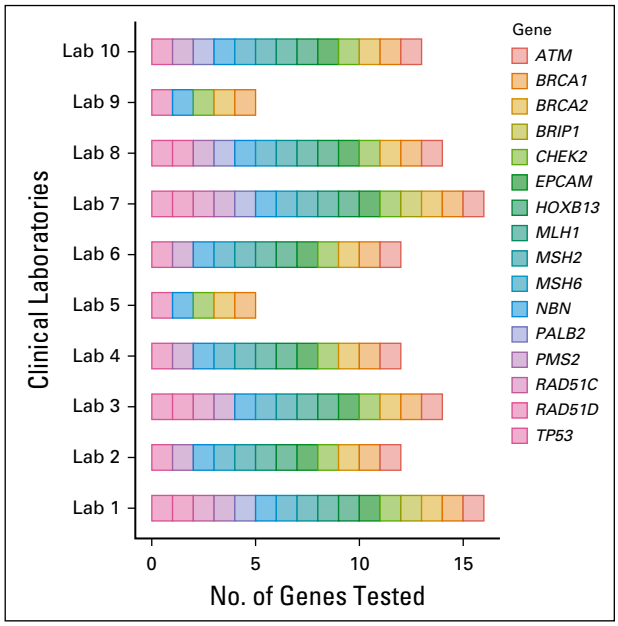

FIG 1. Variability in prostate cancer–specific multigene panels. Genetic testing registry: As of August 2019. Available at: https://www.ncbi.nlm.gov/gtr/. Courtesy of Saud AlDubayan, MD.

Premises based on consensus voting:

- Men should engage in informed decision making for genetic testing (Recommend).
- Building collaborations between health care and genetics providers is important for optimal genetic evaluation (Recommend).

1. Which Men Should Be Considered for Germline PCA Genetic Testing?

Gaps addressed. NCCN guidelines (NCCN Prostate Version 4.2019 and NCCN Breast/Ovary Version 3.2019) at the time of the 2019 Consensus meeting had varying indications for PCA GT.[3,8] Data regarding clinical, pathologic, and FH features were summarized (Data Supplement).

Criteria for testing. Any one of the following criteria may prompt GT:

- **Men with metastatic PCA** (castration resistant or castration sensitive; Recommend).
- **Men with nonmetastatic PCA**—one of the following:
  - Ashkenazi Jewish ancestry (Consider).
  - Advanced disease (T3a or higher; Consider).
  - Intraductal/ductal pathology (Consider).
  - Grade Group 4 (Gleason sum 8) or above (Consider).
- **FH criteria**:
  - **PCA FH criteria**:
    - Men with one brother or father or two or more male relatives with one of the following:
      - Diagnosed with PCA at age < 60 years (Recommend).

- Any of whom died of PCA (Recommend).
- Any of whom had metastatic PCA (Recommend).

○ **FH of other cancers**:

- Two or more cancers in HBOC or Lynch spectrum in any relatives on the same side of the family (especially if diagnosed at age < 50 years; Consider).

Additional considerations. FH consistent with hereditary PCA achieved a strong recommendation for GT. Additional FH criteria were expanded to consider 2 or more cancers in the HBOC or Lynch spectrum to account for limitations in self-reported FH. Genes corresponding to specific cancers are listed in Table 2. Of note, an unremarkable FH does not necessarily negate consideration of GT, particularly for treatment decisions in the metastatic setting.

All pathologic criteria achieved moderate agreement. Universal screening for Lynch syndrome in PCA is not current practice; however, if immunohistochemistry is performed on a prostate specimen revealing loss of the DNA MMR genes, and particularly MSH2, the recommendation is to proceed with GT to determine if the patient has Lynch syndrome given the significant cancer risks and potential treatment implications. Panelists noted that many centers do not report intraductal/ductal pathology or immunohistochemistry for Lynch syndrome markers, which must be addressed with pathologists.

Although multiple unique questions were posed specifically regarding GT for African American men, none met consensus agreement as a result of limited data. Until additional research is completed, testing guidelines as described herein should be applied in under-represented populations.

2. Which Panels Should Be Considered and Which Genes Should Be Prioritized for Testing?

Gaps addressed. Guidance on the use of various gene panels adapted to clinical scenarios is needed given the rapid expansion of panel options and the inclusion of genes with limited association to PCA risk or PCA treatment implications (Fig 1). Furthermore, NCCN guidelines vary regarding genes to test,[3,8] necessitating consensus prioritization of genes for testing (Data Supplement).

Panels considered. Focused—guidelines-based—panels (approximately 5 to 6 genes), PCA-specific panels (approximately 10 to 15 genes), comprehensive cancer panels (approximately 80 genes), and reflex panels (initial set of genes tested followed by broad gene testing) were considered. Benefits and limitations of various panels were also considered (Data Supplement).

Genes considered. *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes were considered.

TABLE 1. Characteristics of Voting Consensus Participants

Participant Characteristic	No. (%)
Primary area of specialty/work (combination of academic and community settings)	
Urology	29 (38)
Medical oncology	13 (17)
Genetic counseling/implementation science	10 (13)
Radiation oncology	5 (7)
Primary care, pathology, and other	9 (12)
Population science/epidemiology	4 (5)
Patient/patient advocate	6 (8)
Geographic region of practice or work	
Northeast United States	26 (34)
Mid-Atlantic United States	14 (18)
Southeast United States	4 (5)
Midwest United States	15 (20)
Southcentral United States	4 (5)
Northwest United States	6 (8)
Southwest United States	3 (4)
Europe, Australia, and Other	4 (5)
Type of region of work	
Urban	55 (71)
Suburban	15 (19)
Rural	2 (3)
Other	5 (6)

TABLE 2. Genetic Contribution to PCA Risk, Aggressiveness, and Proposed Clinical Implications

Gene	Strength of Association for PCA Susceptibility[a]	Risk for Aggressive Disease[a]	Prevalence in Metastatic PCA[b]	Testing for Hereditary Cancer Syndromes and Other Associated Cancers Based on Personal History or FH	Cancer Screening Guidelines for Non-PCAs	PCA-Specific Clinical Impact of Germline Testing: Consensus Conference Summary			
						Implications for PCA Early Detection/PCA Risk Assessment	Implications for AS Decision Making	Metastatic Treatment Options	Clinical Trial Options
ATM	+	++	++	Breast, pancreas	x	+/++	+	++	+++
BRCA1	++	+/−	+	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	++		+++	+++
BRCA2	+++	+++	+++	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	+++	++	+++	+++
HOXB13	+++	–	–	Hereditary PCA		++			
CHEK2	++	+	++	Breast, colon	x				++
MSH2/ MSH6	++	+	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	++		++	+++
MLH1/ PMS2	+	+/−	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	+		++	+++
NBN	+/−	+/−	+	Breast	x				+
PALB2	–	+	+	Breast, pancreas	x				++
RAD51C-D; BRIP1; Fanconi anemia genes	–	–	+	ovarian *(RAD51C/D, BRIP1)*	x				++

Abbreviations: AS, active surveillance; FH, family history; HBOC, hereditary breast and ovarian cancer; PCA, prostate cancer.

[a]Evidence from case-control, familial, cohort, or clinical studies: strong (+++); moderate (++); low (+); conflicting data (+/−); not established (–).

[b]High prevalence (≥ 4%; +++); moderate prevalence (1% to < 4%; ++); low prevalence (< 1%; +); not reported (–).

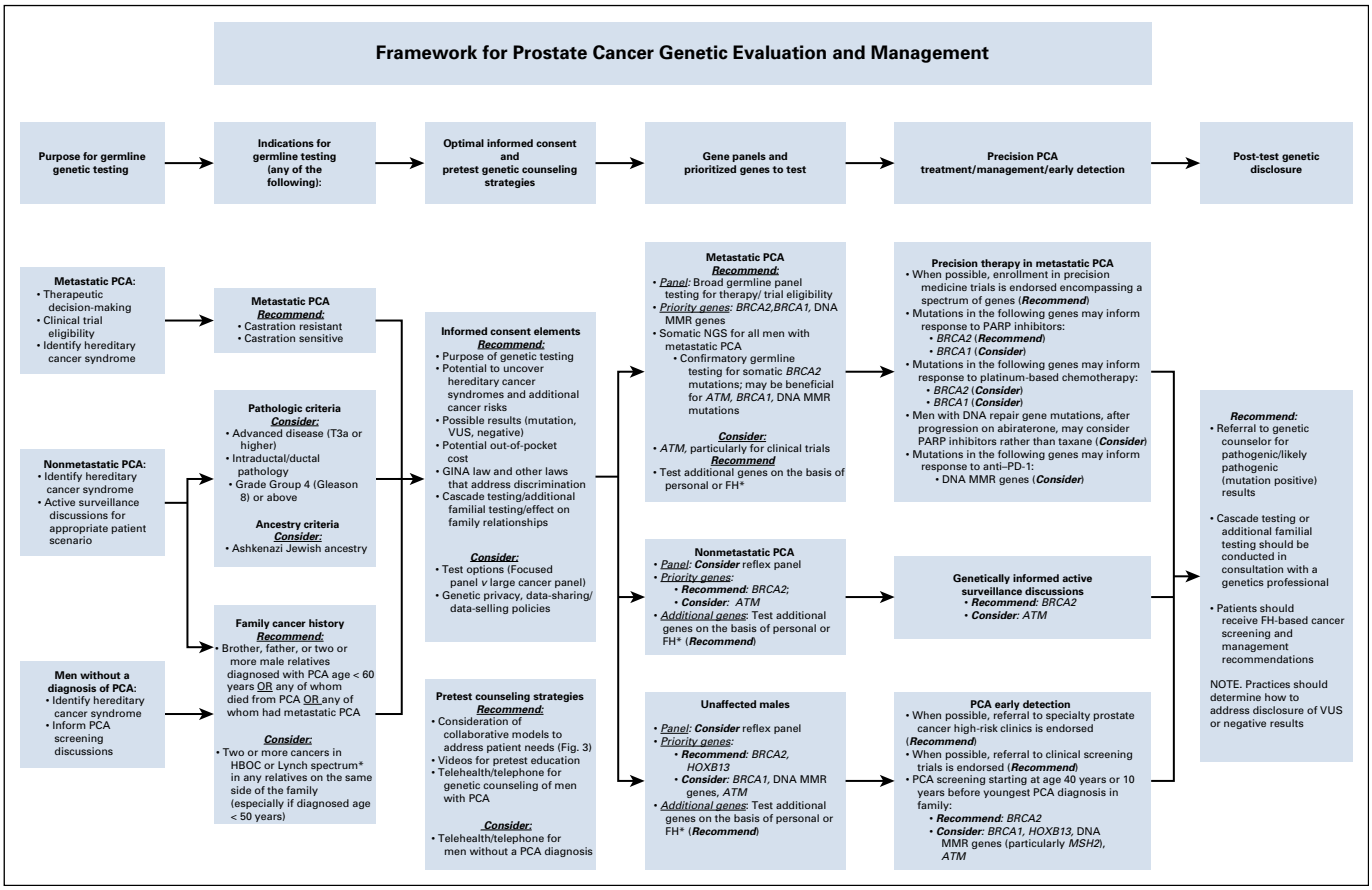

FIG 2. Framework for prostate cancer (PCA) genetic evaluation and management. (*) See Table 2 for personal history or family history (FH) of cancers indicating genes to test. GINA, Genetic Information Nondiscrimination Act; HBOC, hereditary breast and ovarian cancer; MMR, mismatch repair; NGS, next-generation sequencing; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death 1; VUS, variant of uncertain significance.

Panels and genes prioritized for testing:

- **Metastatic PCA**:
  - Comprehensive (large) panel testing for therapy/ clinical trial eligibility (Recommend).
  - **Priority germline testing**:
    - *BRCA2/BRCA1* (Recommend).
    - DNA MMR genes (Recommend).
    - *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Recommend).
  - **Somatic testing**:
    - Somatic next-generation sequencing for all men with metastatic PCA (Recommend).
    - Confirmatory germline testing for somatic mutations:
      - *BRCA2* (Recommend).
      - *BRCA1,* DNA MMR genes, *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).
- **Nonmetastatic PCA**:
  - Reflex testing may be optimal (Consider).
  - Priority genes particularly to inform AS:
    - *BRCA2* (Recommend).
    - *ATM* (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).
- **Men without a diagnosis of PCA meeting FH testing criteria**:
  - Reflex testing may be optimal (Consider).
  - Priority genes for risk assessment:
    - *BRCA2* (Recommend).
    - *HOXB13* (Recommend).
    - *BRCA1, ATM,* DNA MMR genes (Consider).
    - Test additional genes on the basis of personal or FH (Table 2; Recommend).

Additional considerations. For men with metastatic PCA, broader panel testing may be appropriate, particularly if considering treatment or clinical trial options (Table 2, Fig 2, and Data Supplement). Reflex testing may be considered for all patients, but especially for men with nonmetastatic disease considering AS or men without PCA for early detection, which allows for initial testing of genes that inform management (Data Supplement). Reflex testing also allows for testing of additional genes to account for personal cancer or FH at a later time for comprehensive

genetic evaluation and may also be more amenable to collaborative genetic evaluation models (see below).

Among MMR genes, *MSH2* has the strongest association to PCA; however, it is recognized that *MLH1, PMS2, MSH6,* and *EPCAM* also need to be tested to establish the diagnosis of Lynch syndrome. Full MMR testing also may be important for treatment consideration or clinical trials in the metastatic setting; therefore, full Lynch syndrome testing is recommended as indicated.

In addition, confirmatory GT is recommended for men with somatic *BRCA2* mutations and may be beneficial for somatic mutations in *BRCA1,* MMR genes, and *ATM* to identify hereditary cancer predisposition. Additional GT beyond these genes may also be recommended on the basis of personal and FH. Consultation with a genetics professional is advised.

3. What PCA-Specific Recommendations Should Be Considered on the Basis of Genetic Results?

Gaps addressed. There is a need for consensus agreement on genetically informed PCA treatment, management, and early detection[1,2] (Data Supplement). An additional challenge is inconsistency in NCCN genetically based PCA early detection recommendations regarding which genes to consider and the age at which to begin screening[8,9] (Data Supplement).

Genetically based recommendations. Genes considered included *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes.

- **Metastatic PCA**: GT to inform precision therapy:
  - Enrollment of men with PCA in precision medicine trials is endorsed (Recommend).
  - Mutations in the following genes may inform response to PARP inhibitors:
    - *BRCA2* (Recommend).
    - *BRCA1* (Consider).
  - Mutations in the following genes may inform response to platinum-based chemotherapy:
    - *BRCA2* (Consider).
    - *BRCA1* (Consider).
  - Men with DNA repair gene mutations, after progression on abiraterone, may proceed with PARP inhibitor rather than taxane (Consider).
  - Germline mutations in the following genes may inform response to anti–programmed death 1 (PD-1) therapy:
    - DNA MMR genes (Consider).
    - NOTE. The US Food and Drug Administration has granted accelerated approval for anti–PD-1 therapy for microsatellite instability-high/MMR-deficient tumors.
- **Nonmetastatic PCA**: to inform AS discussions:
  - *BRCA2* (Recommend).
  - *ATM* (Consider).
- **Men without a PCA diagnosis to inform PCA early detection**:
  - Referral to specialty PCA high-risk clinics and/or early detection trials was endorsed (Recommend).
  - PCA early detection starting at age 40 years or 10 years before the youngest PCA diagnosis in family:
    - *BRCA2* (Recommend).
    - *BRCA1, HOXB13, ATM,* and DNA MMR genes (particularly *MSH2*; Consider).

Additional considerations. In the metastatic setting, a broad spectrum of genes may be important in determining clinical trial eligibility, and emerging data should continue to refine recommendations. *ATM* garnered consideration for testing, primarily for clinical trial eligibility; however, the panel did not feel that there was sufficient data to endorse *ATM* for informing therapy to PARP inhibitors off study because of the limited independent association to PARP inhibitor response at this time (Data Supplement). *ATM* also garnered moderate consensus for informing AS, but there are limited data at this time (Data Supplement).

For anti–PD-1 therapy, the US Food and Drug Administration has granted accelerated approval for tumors that are microsatellite instability-high or MMR deficient. The panel had moderate consensus regarding a definitive recommendation for anti–PD-1 therapy off study for men with germline MMR mutations, with stronger consideration for clinical trials.

Regarding AS discussions, clinicopathologic criteria, age, and overall health must be considered. *BRCA1* did not achieve consensus for inclusion in AS as a result of limited data for PCA aggressiveness (Data Supplement). Polygenic risk score data were reviewed[77-81] and did not achieve consensus.

4. What Is Optimal Informed Consent for PCA GT?

Gaps addressed. Current practice guidelines do not provide guidance to health care providers regarding optimal informed consent for PCA GT.

Optimal pretest informed consent elements. Ethical considerations of GC were reviewed (Data Supplement). The following elements garnered strong or moderate consensus to discuss with men before GT (Fig 2 and Table 3):

- Recommend discussing: (1) the purpose of GT; (2) the possibility of uncovering hereditary cancer syndromes; (3) potential types of test results; (4) the potential to uncover additional cancer risks; (5) potential out-of-pocket cost; (6) Genetic Information Nondiscrimination Act law and other laws that address genetic discrimination; and (7) cascade testing/additional familial testing.
- Consider discussing: (1) multigene panel options; (2) data sharing/data selling policies of genetic laboratories; and (3) the privacy of genetic tests.

TABLE 3. Priority Elements of Informed Consent for Prostate Cancer Germline Testing

Elements of Informed Consent	Description
Purpose of germline testing	For precision therapy, early detection strategies, and/or to identify hereditary cancer syndrome/risk
Possibility of uncovering hereditary cancer syndromes	Based on FH, testing may include BRCA1 and BRCA2 (associated with hereditary breast and ovarian cancer) or DNA mismatch repair genes (associated with Lynch syndrome; Table 2). Other hereditary syndromes may also be identified.
Panel options	Various multigene panels may be considered for testing (focused PCA panel *v* large cancer panel *v* reflex testing); benefits and risks of each option must be discussed, such as cancer risks uncovered, higher rates of VUS with larger panels, or availability of guidelines for management (Data Supplement).
Potential types of test results	Three main types of results should be discussed, including mutation (pathogenic/likely pathogenic variant), VUS, negative, along with implications of these results on management.
Potential to uncover additional cancer risks	Multiple gene-specific cancer risks may be identified beyond PCA risk that affects men and their families (Table 2).
Potential out-of-pocket cost	Not all insurance plans cover genetic testing for PCA. Some mandate referral to GC. It is important to check with the insurance plan.
Genetic Information Nondiscrimination Act law and other laws that address genetic discrimination	Discuss coverage for health insurance and most employment scenarios. Discuss the lack of coverage for life insurance, long-term care, and disability insurance.
Cascade testing/additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing on the basis of family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patents must be aware of.
Privacy of genetic tests	Protection of genetic data from data breach or access by third parties must be discussed.

Abbreviations: FH, family history; GC, genetic counseling; PCA, prostate cancer; VUS, variant of uncertain significance.

Additional considerations. These elements of pretest informed consent apply to all men who are considering PCA GT[76,82-84] (Fig 2). Such GC aids as handouts or videos may be useful to deliver this information. However, informed consent is a process during which patients have opportunities to ask questions[76,82-84]; therefore, a question-and-answer process must be available before testing. Clinicians without specific training/expertise in GC/GT are urged to refer patients to GC before ordering GT. Furthermore, it is important to remain current on the ethics/informed consent process for GT because of the rapidly evolving nature of precision medicine.

5. What Collaborative Strategies May Facilitate PCA Genetic Evaluation Between Health Care and Genetic Providers?

Gaps addressed. Multidisciplinary guidance on the implementation of collaborative models between health care providers and GC is currently lacking.[103] There is a need to address alternate GC models for timely GT with attention to appropriate pretest informed consent and comprehensive evaluation.

Alternate genetic evaluation delivery strategies. The following strategies were endorsed (Data Supplement and Fig 3):

- Practices should consider multiple models to address patients' needs (Fig 3), including point-of-care models with limited or full pretest FH collection as well as traditional model with upfront referral to GC (Recommend).
- Videos may be useful to deliver pretest informed consent (Recommend).
- In point-of-care models, reflex genetic testing may be optimal to enable additional testing on the basis of personal/FH (Consider).
- Telehealth/telephone delivery of GC is a suitable alternative to in-person GC (Recommend for men with PCA; Consider for unaffected males).

Additional considerations. If limited pretest FH is collected, practices must proactively address the collection of FH in the post-test setting. Reflex testing enables future testing to account for personal/FH. Telehealth/telephone GC was endorsed to address geographic barriers to GC, although patient outcomes data in males are lacking. Key process questions for practices to consider when implementing point-of-care versus traditional GC models were discussed (Data Supplement).

6. What Post-Test Disclosure Strategies Are Most Appropriate Based on Genetic Results?

Gaps addressed. Joint guidance from oncologists, urologists, and genetic counselors for referral to GC is currently lacking.

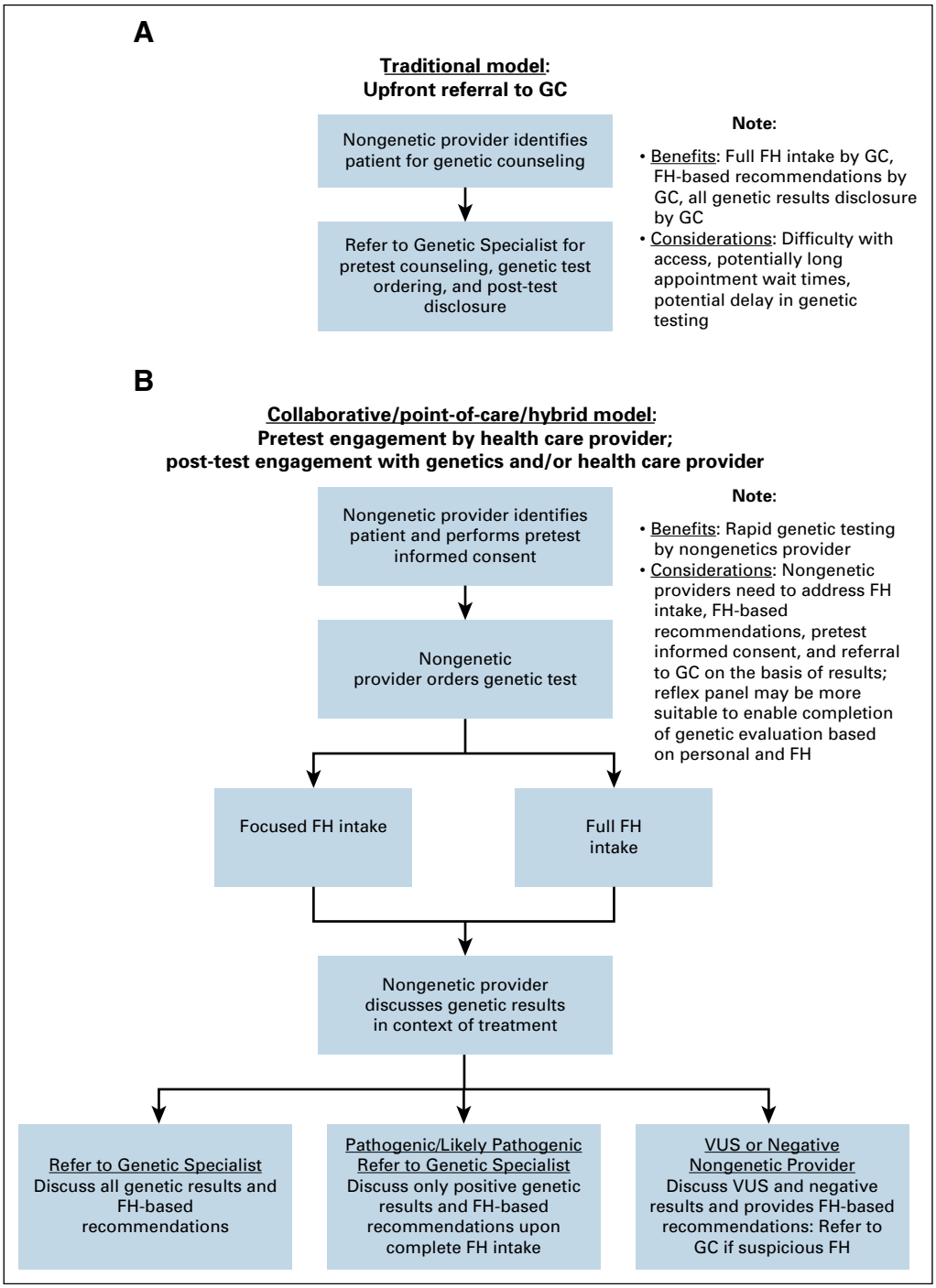

FIG 3. Models of collaboration between genetics and health care practices for prostate cancer genetic evaluation. FH, family history; GC, genetic counseling.

Optimal post-test disclosure strategies:

- Referral to a GC for pathogenic/likely pathogenic results (Recommend).
- Patients should receive FH-based recommendations, either in health care or genetic practices (Recommend).
- Cascade/additional familial testing should be conducted in consultation with a genetic professional (Recommend).

Additional considerations. There was no consensus regarding referral of men with VUS or negative results; therefore, providers will need to determine their ability to discuss VUS results and FH-based recommendations. VUS reclassification to "pathogenic/likely pathogenic" and subsequent management are critical for ordering providers to consider and may support the referral of select men with suspicious VUS to GC. Men with FH of cancers may also warrant referral to GC.

7. What Barriers Must Be Addressed to Enhance PCA GT?

Gaps addressed. Multiple practice, research, and policy gaps pose barriers to PCA GT.

Areas in need of additional attention. The following areas achieved strong or moderate consensus to address:

- Genetic education for providers not formally trained in cancer genetics/genetic counseling (Appendix Table A1, online only, and Data Supplement).
- Barriers to implementation of PCA GT (Appendix Table A2, online only).
- Research priorities (Appendix Table A3, online only).

DISCUSSION

As GT for PCA has rapidly increased, responsible implementation of testing and management are of primary concern.[1,2,19,23] Current practice challenges that pose barriers to operationalizing PCA GT include the variability in testing indications and genetically based management, the need for guidance on panels and priority genes to test, and guidance regarding alternate evaluation models to address GC demand. The 2019 Philadelphia Prostate Cancer Consensus Conference was a focused attempt to address these critical challenges and practice gaps by developing a first-in-field working framework for PCA genetic evaluation, management, and implementation informed by best evidence and expert guidance.

The strength of the consensus framework is the creation of a unified approach regarding GT indications, genetically informed management and treatment, and the integration of GC. Multiple aspects of the framework had strong evidence and strong expert agreement to deem a definitive action of "Recommend". The strongest recommendations encompassed testing all men with metastatic PCA or men with FH suggestive of hereditary PCA. Priority genes for testing included *BRCA2, BRCA1*, and the DNA MMR genes in metastatic disease to inform treatment or clinical trials; *BRCA2* for AS discussions; and *BRCA2* and *HOXB13* for PCA early detection discussions. This was the first formal, multidisciplinary endorsement for broad panel testing among men with metastatic PCA, recognizing that genetic information may enable men to enroll in clinical trials. Consensus emerged regarding strategies for PCA early detection on the basis of genetic status. For male carriers of *BRCA2*, a recommendation was made to begin PSA screening at age 40 years or 10 years before the youngest PCA diagnosis in a family and is modeled after colorectal cancer guidelines.[16]

An important aspect to the genetic evaluation framework was the integration of care processes and GC to account for the increasing need for GC. Strong recommendations were made for optimal pretest informed consent. Recommended strategies to deliver GC included collaborative GC models, videos, and telehealth to facilitate GT through health care practices and to collaborate with GC. Reflex testing garnered moderate consensus and may be considered, particularly when using collaborative counseling models to enable upfront testing by health care providers, followed by testing additional genes using GC for comprehensive genetic evaluation. In the post-test setting, strong recommendations were made to refer all men with pathogenic mutations to GC, to conduct cascade testing of relatives under the care of genetics professionals, and to determine the delivery of FH-based recommendations.

The panel dealt with many uncertainties in recommendations which garnered moderate consensus. Whereas many genes have a lower level of evidence for PCA risk, aggressiveness, or treatment response, several clinically available multigene panels include lower evidence genes. To indicate these nuances in limited data or moderate consensus, many criteria were designated as "Consider" in the framework. Pathologic criteria for testing, such as disease stage, intraductal/ductal histology, or Grade Group ≥ 4, garnered moderate consensus and therefore are included as suggestive criteria for testing.[63,65,66] Ashkenazi Jewish ancestry as a standalone criterion achieved moderate consensus, but may be a stronger consideration for testing for men with higher Gleason score per current NCCN guidelines.[8] Whereas PCA has been linked with HBOC and Lynch syndrome, a working definition of familial features that increase the likelihood of detecting germline mutations is needed. As such, having two or more relatives with cancers in the HBOC or Lynch syndrome spectrum garnered moderate consensus as standalone criteria and may be considered for GT on the basis of patient preference and insurance coverage.

Priority genes to test also presented challenges, particularly regarding *ATM*, DNA MMR genes, and *HOXB13*. Initial data have reported that men with *ATM* mutations experienced clinical response to PARP inhibitors[94]; however, follow-up studies have reported a limited independent effect of *ATM*.[99] Similarly, studies in AS had limited association of *ATM* mutations alone with upgrading of biopsies.[7] Until additional data are available, *ATM* was given a designation of "Consider" for testing, recognizing the potential for clinical trial options for *ATM* carriers. Additional uncertainties were encountered regarding prioritizing MMR genes for GT. Among MMR genes, *MSH2* has the highest reported association to PCA.[41] Although other MMR genes have lower or limited association to PCA, the potential to uncover Lynch syndrome and clinical trial eligibility drove the suggestion to consider full Lynch syndrome testing. *MSH2* status may be more informative for PCA early detection discussions.[41] *HOXB13* has strong association to PCA risk and early-onset disease, though screening outcomes data are limited. Therefore, the consensus panel recommended testing for *HOXB13* and to consider the results in early detection discussions. Overall, *BRCA1, HOXB13*, and MMR genes were designated as "Consider"

for beginning screening at age 40 years or 10 years before the youngest PCA diagnosis in the family because of the currently limited screening data.[9] Data from screening studies, such as IMPACT and the National Cancer Institute (ClinicalTrials.gov identifier: NCT03805919), will be important to reconsider strengthening these recommendations.[10] However, this is the first time that screening strategies based on a larger genetic spectrum have been proposed. Additional research in African American males is vitally needed. Future consideration of circulating tumor and cell-free DNA is also warranted.

In conclusion, the 2019 Consensus Conference created the first multidisciplinary PCA genetic implementation framework tailored to the precision medicine era. The framework, which importantly had input from NCCN panel leaders, provides guidance to a spectrum of providers to facilitate timely and responsible PCA GT for the benefit of men and their families.

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APPENDIX

TABLE A1. Priority Topics for Provider Education

Area of Knowledge	Percent Agreement
Recommend	
Purpose of genetic testing	100
Understanding types of results (mutation, VUS, negative)	92
Genetic Information Nondiscrimination Act and other laws that address discrimination	89
Hereditary cancer syndromes (HBOC, Lynch syndrome, HPC) that may be uncovered	86
Test options (focused prostate cancer panel *v* large cancer panel)	86
Additional cancer risks that may be uncovered	84
Potential out-of-pocket costs for genetic testing for patients	84
Privacy considerations of genetic tests	78
Cascade testing/additional familial testing/effect on family relationships	76
Consider	
Choice of laboratory for testing (pros and cons of test accuracy)	68
Data-sharing/data-selling policies of laboratories	62

NOTE. The Data Supplement provides educational resources for providers or trainees regarding germline testing.
Abbreviations: HBOC, hereditary breast and ovarian cancer; HPC, hereditary prostate cancer; VUS, variant of uncertain significance.

TABLE A2. PCA Genetic Testing Implementation Barriers

Barrier	Percent Agreement
Recommend	
Increase advocacy and public awareness for PCA genetic testing and impact of genetic results for men and their families	99
Reimburse telehealth and telephone counseling	98
Implement virtual tumor boards, virtual molecular boards, or virtual genetics boards to disseminate genetics and molecular expertise	79
Redefine “actionability” to include familial impact of genetic testing for payer coverage	75
Consider	
Increase lobbying efforts to enhance payer coverage of PCA genetic testing	64
Engage primary care providers in genetic evaluation for PCA	63

Abbreviation: PCA, prostate cancer.

TABLE A3. Research Priorities to Advance PCA Genetics Knowledge and Practice

Priority Area	Percent Agreement
Recommend	
Genetics of PCA in diverse populations of men	93
Clinical outcomes by germline mutation status	93
Precision medicine trials	88
Precision PCA early detection trials	80
Basic science research into metastatic disease biology	76
Consider	
Implementation outcomes research regarding the alternate delivery of genetic counseling	72
Psychosocial outcomes of men undergoing genetic testing through various clinical approaches	63

Abbreviation: PCA, prostate cancer.