

## Clinical features and management of *BRCA1* and *BRCA2*-associated prostate cancer

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## 1. ABSTRACT

It is thought that over forty percent of an individual's risk of developing prostate cancer (PCa) is related to familial and genetic factors. Although multiple genes have been implicated in the development of PCa, few confer as high a risk as mutations in the genes associated with early-onset breast cancer (*BRCA1* and *BRCA2*). Not only do mutations in *BRCA* genes increase the risk of PCa, but they have also been related to adverse disease characteristics and outcomes. Therefore, a better understanding of the association between *BRCA* gene mutations and PCa may provide the backdrop for individualized management of patients with PCa who are carriers of a gene mutation. Such management may include an individualized approach to screening and treatment including chemotherapeutic regimens targeted to the underlying genetic mechanism of disease. In this paper, we review the evidence relating *BRCA* gene mutations to the risk of PCa, as well as outcomes and response to therapy, and suggest an approach to the management of such patients.

## 2. INTRODUCTION

Of all the potential risk factors examined for PCa, genetic predisposition has been validated across multiple studies. Family history of PCa is one of the strongest risk factors for the disease: individuals with first-degree relatives affected by PCa have double the lifetime risk of developing PCa compared to the rest of the population. In addition, twin-based registries have demonstrated that approximately 40% of this risk can be explained by inheritance.(1, 2) More recently, genome-wide association studies and next-generation targeted sequencing of specific regions of the genome identified through familial linkage studies have enabled researchers to successfully identify genetic variants (such as *HOXB13*) that are associated with hereditary PCa.(3)

The association between *BRCA* genes and PCa has been well documented. Inherited mutations in *BRCA1* and *BRCA2* have been associated with a significantly increased risk of developing PCa. This risk of PCa is increased 3.5-fold in carriers of the *BRCA1* mutation (4)

and 8.6-fold in carriers of *BRCA2* mutations who are younger than 65 years of age. (5) The lifetime risk of developing PCa is estimated to be 9.5% for carriers of a *BRCA1* mutation (4) and 20% for *BRCA2* mutation carriers. (6) Mutations in *BRCA1* and *BRCA2* have also been associated with more aggressive features and worsened outcomes. (7, 8)

In an age of personalized cancer medicine, patients with specific hereditary risks should receive individualized recommendations for prevention that exploit the unique genetic characteristics of their disease. Our goal in this paper is to review the available evidence on the association between *BRCA* mutations and PCa, including disease characteristics and response to therapy, and to suggest a plan for the management of patients whose disease characteristics suggest *BRCA* mutations as an underlying risk factor.

### 3. MECHANISMS UNDERLYING BRCA GENE-RELATED CARCINOGENESIS AND METASTASIS IN PCA

*BRCA* genes are autosomal dominant cancer-susceptibility genes that show incomplete penetrance. They are generally understood to function as tumor suppressor genes; for carcinogenesis to occur in carriers of *BRCA* germline mutations there is typically loss of the wild-type allele. Of the two genes, *BRCA1* appears to have a larger role in some cellular processes, including repair of DNA damage, regulation of protein transcription, and epigenetic effect on genomic stability. (9, 10) The role of *BRCA2* appears to be limited to repair of DNA damage by regulating the function of other proteins, such as RAD51. (9) It is plausible that mutations in these genes leading to dysfunction in DNA repair pathways could increase the risk for PCa, but exactly how mutations in *BRCA* genes affect the course of the disease is not well understood. *BRCA1* has been shown in PCa cell lines (PC-3) to be involved in regulating pathways that are active in PCa such as the androgen receptor pathway (11) and the insulin-like growth factor 1 (IGF1) receptor pathway. (12) For *BRCA2*, the available evidence suggests that its functional loss affects both the focal development of PCa (through loss of its tumor suppressor function in the prostate epithelial tissue) (13) and the potential for the disease to spread through upregulation of matrix metalloproteinase-9 by modulation of the PI3-kinase/AKT and MAP/ERK signaling pathways. (14)

### 4. ASSOCIATION BETWEEN BRCA GENE MUTATIONS AND PCA RISK

The evidence to support the association of *BRCA* mutations with PCa risk is based on retrospective studies involving multi-institutional registries of families affected by these mutations, or big cohorts of PCa patients. Thompson *et al.* conducted a cohort study of 11 847 individuals from 699 families segregating a *BRCA1* mutation that were ascertained in 30 centers across Europe and North America. He then reported an 82% increase in the risk of PCa in *BRCA1* mutation carriers, but this effect

was limited to men younger than 65 years of age, (15). The Breast Cancer Linkage Consortium investigated the risk of other cancers in 173 breast-ovarian cancer families with *BRCA2* mutations identified at 20 centers in Europe and North America. Other cancer occurrence was determined in a final cohort of 3728 individuals, among whom 681 persons had breast or ovarian cancer and 3047 persons either were known mutation carriers, were first-degree relatives of known mutation carriers, or were first-degree relatives of breast or ovarian cancer patients. The Consortium found that carriers of *BRCA2* mutations had a 4.65-fold relative risk of developing PCa, with the risk being highest (7.33-fold) in men younger than 65. (6) Two recently published studies from the United Kingdom also reported an increased relative risk of developing PCa before age 65. Leongamornlert *et al.* screened 913 cases aged 36–86 years for germline *BRCA1* mutation, with the study enriched for cases with an early age of onset, and analyzed the entire coding region of the *BRCA1* gene using Sanger sequencing. In that study, using previously estimated population carrier frequencies, the authors concluded that deleterious *BRCA1* mutations confer a relative risk of PCa of about 3.75-fold, (95% confidence interval (CI)=1.02 to 9.60) translating to a 8.6% cumulative risk by age 65. (4) In a similar study, Kote-Jarai screened *BRCA2* for variants in 1864 men with PCa aged between 36 and 88 years and noticed 8.6-fold increase in PCa risk in *BRCA2* mutation carriers. (5) Finally, in a study from our institution, Gallagher *et al.* genotyped 832 Ashkenazi Jewish men with localized PCa between 1988 and 2007 and 454 Ashkenazi Jewish controls for two founder mutations. (16) They reported that *BRCA2* mutations were associated with a 3-fold increase in the risk of PCa (95% CI=1.52 to 6.66).

### 5. ASSOCIATION BETWEEN BRCA GENE MUTATIONS AND PCA CLINICAL CHARACTERISTICS

The association of *BRCA* mutations with aggressive PCa characteristics is generally based on small retrospective studies. Using population-based registries, Tryggvadottir *et al.* identified all 596 PCa patients who were diagnosed in Iceland during 1955 through 2004 among 29603 male relatives of unselected breast cancer probands. They then abstracted stage and grade for a subgroup of 89 patients that included all mutation carriers and, for each carrier, two non-carriers who were matched to the carrier on years of diagnosis and birth. Compared with non-carriers, *BRCA2* 999del5 mutation carriers had a lower mean age at diagnosis (69.0 years versus 74.0 years;  $P = .002$ ), more advanced tumor stage (stages 3 or 4, 79.3% versus 38.6%;  $P < .001$ ), higher tumor grade (grades G3–4, 84.0% versus 52.7%,  $P = .007$ ), and shorter median survival time (2.1 years, 95% CI = 1.4 to 3.6 years, versus 12.4 years, 95% CI = 9.9 to 19.7 years). *BRCA2* 999del5 mutation was also associated with an increased risk of dying from PCa (adjusting for year of diagnosis and birth, hazard ratio (HR) 3.42, 95% CI = 2.12 to 5.51); the association remained after adjustment for stage and grade (HR = 2.35, 95% CI = 1.08 to 5.11). (17) These poorer outcomes have also been seen in association with the

Ashkenazi Jewish founder mutations, *BRCA1* 185delAG and *BRCA2* 6174delT. Gallagher *et al* compared clinical outcome measures among 26 *BRCA* mutation carriers and 806 non-carriers and reported a 28% increase in the risk of developing poorly differentiated tumors (Gleason score  $\geq 7$ ) compared with non-*BRCA*-associated PCa. Carriers of either mutation had a higher risk of recurrence (HR 4.32, 95% CI=1.31 to 13.62 for *BRCA1*; and HR 2.41, 95% CI=1.23 to 4.75 for *BRCA2*) and PCa-specific death (HR 5.16, 95% CI=1.09 to 24.53 for *BRCA1*; and HR 5.48, 95% CI=2.03 to 14.79 for *BRCA2*) than non-carriers.(16) The authors did not find significant difference in age at presentation between *BRCA2* mutation carriers and non-carriers (HR 1.23, 95% CI 0.76-2.00) nor between *BRCA1* mutation carriers and non-carriers (HR 0.67, 95% CI= 0.28 to 1.61). Few studies have examined the effect of *BRCA* mutations on the outcome of PCa. Edwards *et al* found a difference of 4 years in median overall survival between *BRCA2* carriers and non-carriers with PCa.(18) Thorne *et al* showed that carriers of *BRCA2* mutations have worse PCa-specific survival (HR 4.97, 95% CI=2.19 to 11.25), though that could be a function of a much higher percentage of undifferentiated (Gleason  $\geq 8$ ) tumors (65.8% vs. 33.0%) and pT3–T4 tumors (39.5% vs. 22.6%) in their cohort of carriers compared with non-carriers.(19) Narod *et al* observed that the 5-year overall survival was shorter for carriers of *BRCA2* than *BRCA1* (42% vs. 64%, respectively), with a median overall survival of 15 years for *BRCA1* mutation carriers and 5 years for *BRCA2* mutation carriers.(20) Finally, Castro *et al* investigated clinical characteristics and outcomes in 2181 patients with PCa, of whom 5 were carriers of *BRCA1* and 31 were carriers of *BRCA2* germline mutations.(21) The authors reported a wide spectrum of pathogenic mutations conferring a more aggressive PCa phenotype (Gleason  $\geq 8$ : *BRCA2* 50%, *BRCA1* 20%, non-carriers 21%;  $P = 0.017$ ), a higher incidence of lymph node involvement (N1: *BRCA2* 35%, *BRCA1* 50%, non-carriers 11%;  $P < 0.001$ ), and a higher likelihood of distant metastasis at diagnosis (M1: *BRCA2* 21%, *BRCA1* 20%, NC 9%,  $P = 0.034$ ). Also, compared with non-carriers, patients with *BRCA2* mutations had significantly shorter overall survival (10.8 vs. 13.3 yrs, respectively, HR 2.5,  $P < 0.001$ ) and cancer-specific survival (8.6 vs. 16.3 yrs, HR 2.8,  $P < 0.001$ ).

### 6. BRCA STATUS AND RESPONSE TO MEDICAL THERAPY FOR PCA

To our knowledge, only one small size retrospective study has investigated the effect of *BRCA* mutations on patients' response to taxanes for treatment of PCa. Gallagher *et al* (22) determined *BRCA* mutation prevalence in 88 Ashkenazi Jewish men with castration-resistant PCa and examined their response to taxane-based therapy, as measured by the PSA nadir within 12 weeks of therapy. The authors did not find a significant difference in response to taxanes between carriers (57% of whom responded) and non-carriers (72% responded) (absolute difference 15%; 95% CI= 23% to 53%;  $P = 0.4$ ). The authors of that study found it interesting, however, that the one *BRCA2* carrier treated with docetaxel plus carboplatin survived 37 months, more than twice as long as other

mutation carriers. The authors then suggested that since *BRCA* mutations inactivate homologous DNA repair, they could render cells sensitive to DNA-targeting agents such as cisplatin and carboplatin and lead to prolonged survival of patients treated with these medications. (23)

Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme important in base excision repair of single-stranded DNA breaks. (24) Inhibition of PARP leads to the accumulation of single-strand breaks that eventually lead to double-strand breaks. Cells deficient in *BRCA* are unable to repair these double-strand breaks, and their exquisite sensitivity to PARP inhibition results in cell cycle arrest and cell death. The only clinical trial that investigated PARP inhibitors in PCa patients affected by *BRCA* mutations was a phase I trial by Fong *et al*. In that trial, PARP inhibitor (olaparib) was used to treat *BRCA* mutation carriers affected by different malignancies, three of whom had PCa. One patient, with a *BRCA2* mutation and castration-resistant PCa, had a greater than 50% reduction in his PSA level, resolution of bone metastases, and was still participating in the study at 58 weeks' follow-up. (25)

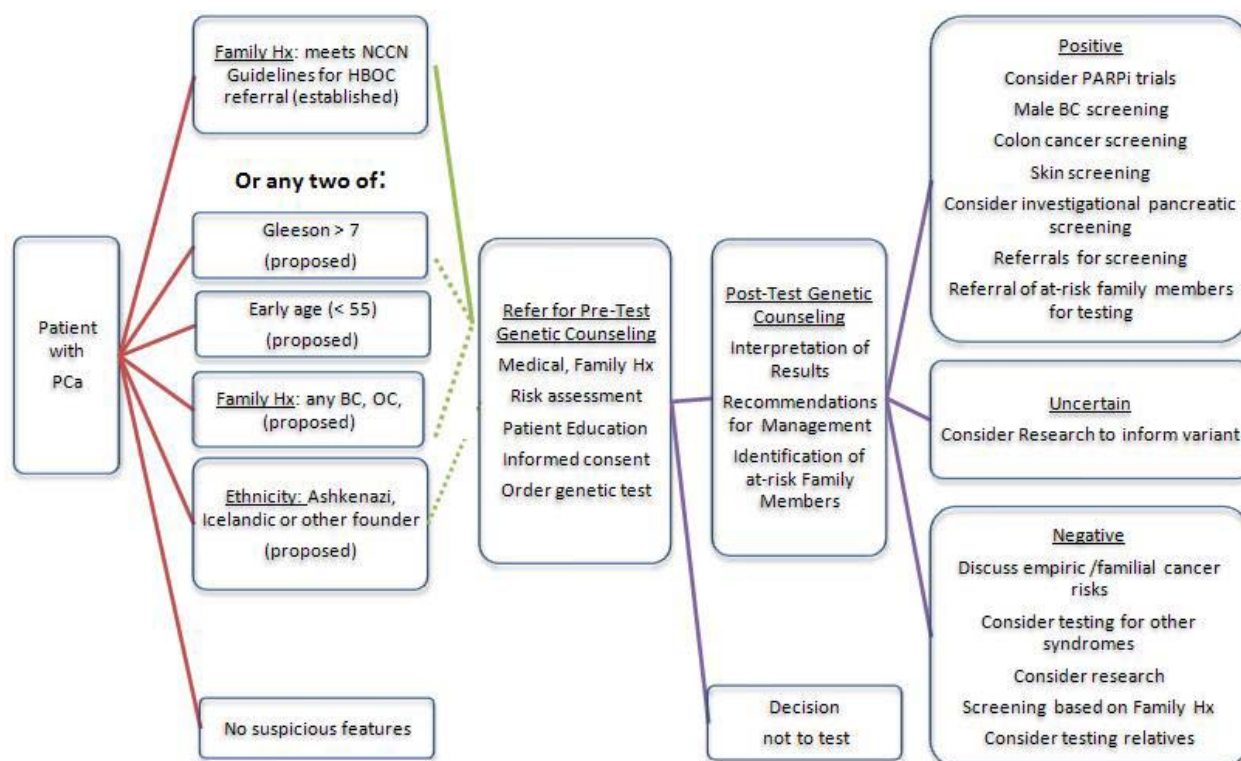
Finally, next-generation hormone ablation therapies, such as abiraterone and enzalutamide, are showing survival benefit in castration-resistant PCa, as evidenced by large randomized controlled trials. (26, 27) There is no data to support dysregulation of androgen receptor pathway in PCa tissue from *BRCA* mutation carriers. . Berns *et al* analyzed breast tumor tissue from *BRCA* mutation carriers for androgen receptor expression and found that the androgen receptor was present in only 12% of *BRCA1*-mutated tumors. Androgen receptor expression was significantly more prevalent in a series of 61 sporadic breast tumors (80%) and in *BRCA2*-mutated tumors (50%) included in the same study.(28) Further research into the association between *BRCA* mutation status, AR expression, and treatment response to next-generation hormone ablation may help individualize hormonal therapy for patients with PCa who are *BRCA* mutation carriers.

### 7. SELECTION OF CANDIDATES ELIGIBLE FOR GENETICS REFERRAL

#### 7.1. Current referral patterns and existing guidelines

Asymptomatic individuals in the general population are not currently screened for *BRCA1* and *BRCA2* mutations because of the low overall prevalence, which is approximately 1 in 800, or 0.125%.(29, 30) Existing guidelines for *BRCA1/2* testing are based on having a personal history of early breast or ovarian cancer, or a family history of multiple cases of these cancers, (31) due to an increased frequency of mutations in those populations.(32) A widely used set of criteria provided by the National Comprehensive Cancer Network (NCCN)(33) (Figure 1), recommends *BRCA* testing for all men with breast cancer, all women with ovarian cancer, a subset of women with breast cancer (early onset, triple negative, or multiple cases within a family), and unaffected individuals with a family history of these tumors. Other professional organizations and health programs such as the American

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**Figure 1.** Proposed selection of prostate cancer patients for referral to BRCA genetic counseling.

Society of Clinical Oncology (ASCO), (34) American College of Medical Genetics (ACMG) (35) and the U.S. Preventive Services Task Force (USPSTF) (36) have developed referral criteria for *BRCA* genetic evaluation. (37) Most include questions about personal and family history of *BRCA* mutations, breast cancer, ovarian cancer, age of diagnosis, bilateral breast cancer, and Ashkenazi Jewish ancestry. However, with the exception of male breast cancer, these guidelines all focus on eligibility requirements for testing of female candidates. The USPSTF, American College of Obstetrics and Gynecology (ACOG), and Society of Gynecologic Oncologists (SGO) recommendations apply exclusively to women. Both the ACOG (29) and the SGO (38) use personal and family history of cancer to define groups at risk of developing the breast and ovarian cancer syndrome. A genetic risk assessment is “recommended” for women with a 20%–25% risk of developing the syndrome, and “may be helpful” for women with a 5%–10% risk—but no such recommendations apply to men potentially at risk of developing a *BRCA*-related cancer. Many third-party payers have developed variations of these criteria for coverage of testing. Medicare coverage of genetic testing is limited to women personally affected with breast or ovarian cancer, and men affected with breast cancer. (39) Other payers cover individuals who are currently unaffected by cancer, provided the family history is sufficient. However, these criteria are dynamic—for example; the NCCN criteria are reviewed and updated annually by a panel of experts. A personal or family history of pancreatic cancer has recently been introduced into the NCCN guidelines and, when other criteria are met, may determine eligibility for testing.

Medicare and other payers have been known to modify their policies in accordance with NCCN guidelines.

### 7.2. Limitations of current referral practices

The importance of referring men for genetic counseling and testing has been viewed as under-recognized in current guidelines and under-studied in the literature. (40) None of the abovementioned guidelines acknowledge a history of PCa, despite the fact that male carriers of *BRCA* mutations are clearly at increased risk for the disease. (41) Due to the variability in clinical presentation, *BRCA*-positive families have been described that have a predominance of PCa, over other *BRCA*-related malignancies. (42) Because of their autosomal dominant inheritance pattern, the rate of transmission of *BRCA* mutations through fathers (43) or mothers is equivalent. The strategy to include first-degree relative pairs with prostate and breast cancer in guidelines generated discussion at a large consensus conference in 2007, (44) but no final recommendation was made. Even in families with known *BRCA1/2* mutations, male relatives have been shown to be less likely to be informed of their risk. (45–47) These men, and their providers, may not realize the implications of female relatives’ diagnoses of breast and ovarian cancer. Although public awareness of *BRCA* testing has increased with direct-to-consumer marketing, (48–50) these campaigns are focused on the implications for females at risk for breast and ovarian cancer. It is, therefore, not surprising that men do not perceive a personal relevance, and do not come forward for genetic assessment. (51) .

### 7.3. Importance of recognizing males at risk for BRCA mutations

Consideration should be given to the importance of a full genetics evaluation, including risk for *BRCA* mutations for men, especially those affected with breast, pancreas, or PCa. Until recently, knowledge of *BRCA* status would not have influenced disease treatment, but this is changing with the advent of new therapeutics. These men should also be made aware of their risk of developing other *BRCA*-associated cancer types, and available screening should be offered. (52) Finally, this information is highly relevant to their family members, especially daughters and sisters. Healthcare providers for men with PCa, such as urologists, medical oncologists, oncology nurses, and primary care physicians, are in a unique position to identify candidates for genetic counseling and testing, since they routinely collect information about disease status, ethnicity and family history. Online tools, such as “My Family Health Portrait,” are also available for patients to use to collect their own family health information, (53, 54) and they should be encouraged to do so. (55)

### 7.4. Potential improvements in selection criteria

The prevalence of *BRCA1/2* mutations in unselected men with PCa is not high, and may not justify genetic screening of all such men. Given the suggested 3.18 fold increase in the relative risk of PCa due to *BRCA2* mutations, and the 0.0069 *BRCA2* mutation frequency in the population, it could be estimated that 1.5% of the 241,000 PCa cases diagnosed yearly in the United States may be attributable to *BRCA2* mutations, or about 3,626 cases per year. (16) (6) The situation is comparable to that of unselected female breast cancer cases, for which *BRCA* mutation screening of the general population is also not recommended. As with the breast cancer group, it may be possible to identify subgroups of men with PCa that are enriched for *BRCA* mutations based on age of diagnosis, tumor characteristics, family history, and/or ethnicity. Kote-Jarai *et al* found a 1.2% frequency of *BRCA2*-specific mutations in men diagnosed with PCa in the United Kingdom before the age of 66, (56) while a 2.3% frequency was found in those diagnosed younger than age 55. (57) The strongest predictors for the presence of a *BRCA2* mutation were a young age of PCa onset and a family history of breast and/or ovarian cancer. No mutations were detected in 243 men diagnosed over age 65, even though they also had a family history of PCa. A study of 886 men with PCa enriched for early-onset disease found 4 (0.45%) *BRCA1* mutation carriers, (58) suggesting an even higher prevalence when screening for both *BRCA1* and *BRCA2*. In a study of 290 men in the United States diagnosed with PCa before age 55, 0.8% carried mutations. (59) By comparison, some groups of women who meet the NCCN criteria for *BRCA* testing have an even lower risk of a mutation. For example, using the Tyrer-Cuzick risk estimation model, a 55-year-old woman without cancer whose mother had breast cancer after age 45 has less than a 0.5% risk of carrying a *BRCA* mutation. (60) If her mother had ovarian cancer at age 65, her risk would be 0.9%. In both cases, the proband would be eligible for *BRCA* testing by most guidelines.

Founder mutations in *BRCA1* and/or *BRCA2* are known to be highly prevalent in many ethnic groups, including those of Ashkenazi Jewish, (61) Swedish, (62) Hungarian, (63) Icelandic, (64) Dutch, (65) or French-Canadian (66) descent. Of unselected Icelandic PCa patients, 3% were found to carry the founder mutation in *BRCA2*. (67) In the Ashkenazi Jewish population, between 1% and 2.5% (1 in 40) have a founder mutation in *BRCA1* or *BRCA2*. (61, 68) Some authors have even started a discourse about *BRCA1/2* screening of all individuals in this ethnic group, regardless of cancer history. (43, 69) Potential problems with this approach, however, may include decreased cancer risks in mutation carriers detected through population screening as opposed to at high-risk clinics. (70) In 251 Ashkenazi men with PCa, 13 (5%) had a deleterious mutation in *BRCA1* or *BRCA2* compared with 28 (1.9%) unaffected controls. (71) In a study of 979 Ashkenazi Jewish patients with PCa, 3.0% had a *BRCA* founder mutation, versus 1.8% of unaffected controls. (72) A population-based study of 940 paraffin specimens from Ashkenazi patients included in the Israeli Population Registry detected an overall prevalence of the 3 common founder mutations of 3.2%, compared with a reference group of 1.6%. (73) Similarly, in Gallagher *et al*, 3.1% of Ashkenazi patients with PCa carried either a *BRCA1* or *BRCA2* founder mutation. (16) Other studies did not find an increased prevalence of mutations in unselected Ashkenazi men with PCa over the population risk, (74-78) although those studies were small.

Selecting affected men with two of these risk criteria (such as ethnicity and family history) may serve to further enrich the group. In the study of Ashkenazi men with PCa by Agalliu *et al*, (72) the prevalence of mutations was higher (5%) in men with a first-degree family history of breast and/or ovarian cancer, although a family history of PCa did not further increase the risk. In a population-based study by Tryggvadottir *et al*, 30 out of 527 men (5.7%) with PCa who were relatives of unselected women with breast cancer carried the Icelandic *BRCA* founder mutation. (17) These frequencies meet the lower threshold of risk for women defined by ACOG and SGO as those for whom genetic risk assessment may be helpful. In Icelandic families known to carry the *BRCA2* mutation, 8 out of 12 male relatives (67%) with PCa had the founder mutation. (67)

Although studies to date are limited, there is no clear link between *BRCA* mutations and familial PCa. One study did report a prevalence of 5% (2 of 38 families) for *BRCA2* protein truncating mutations in hereditary PCa families, with two to five affected men per family. (79) No relevant variants were detected in *BRCA1*. Importantly, the 13 families with multiple cases of site-specific PCa did not carry detectable *BRCA* mutations. The 2 identified *BRCA2* carriers were diagnosed with PCa at ages 54 and 56. One had a mother with pancreatic cancer, and the other had a mother with postmenopausal breast cancer. Surprisingly, both carriers had a younger affected brother who did not carry the familial *BRCA2* mutation. This suggests the possibility of phenocopies and/or co-segregation of other (modifier) alleles, both of which would complicate genetic

counseling and testing. Several additional studies (reviewed by Alvarez-Cubero *et al*) have not documented a major role for *BRCA2* in explaining familial PCa.(80) Wilkens *et al.* found no *BRCA2* mutations among 18 Ashkenazi Jewish men, each having at least three first-degree relatives affected with PCa; although one unaffected man carried the 6174delT mutation in *BRCA2*.(81) Sinclair *et al.* found no *BRCA2* protein-truncating mutations in 43 individuals from 22 hereditary PCa families, each with at least three affected men and two or more breast and/or ovarian cancers .(82) They did find a missense mutation and 2 novel polymorphisms. The PCa Genetic Research Study in Seattle examined 194 hereditary PCa families, and found no truncating *BRCA2* mutations.(83) They did find 31 missense variants, although no associations were found between these and family characteristics. Similarly, no *BRCA2* truncating mutations were found in 5 Utah high-risk PCa pedigrees that had strong linkage evidence near the *BRCA2* gene region on chromosome 13q. One *BRCA2* variant of uncertain significance was non-segregating. (84) However, the authors noted an unexplained linkage to chromosome 13q (the locus of *BRCA2*) that could not be attributed to identifiable *BRCA2* mutations. They speculated that occult *BRCA2* mutations or other nearby PCa susceptibility genes, such as *HMG1*, *LGR8*, *CCNA1*, *TRPC4*, and *FOXO1* may be involved. Overall, families with site-specific PCa may be a heterogeneous group, with contributions from multiple genes other than *BRC1* and *BRCA2*, unexplained factors, and exogenous and endogenous environmental factors. (80) At least 30 *loci* have been suggested by genome-wide association studies (GWAS). Even if these families are not now clinical candidates for germline *BRCA* testing, it may still be prudent to identify this group moving forwards. As molecular genetics research evolves, characterization of other related genes may better inform genetic counseling for these families.

In view of these data, a potential schema for referral and a genetics workup for men with PCa is shown in Figure 1. Men who meet the existing NCCN guidelines are already eligible for a genetics workup, and providers should be alert to identify them. In this schema, men with two potential risk factors, including high Gleason score (>7), early age of diagnosis (<55), relevant ethnic background (especially Ashkenazi ancestry or Icelandic origin), or any close family member with breast or ovarian cancer, may be referred for genetic counseling. Based on their case report, Taherian *et al.* have suggested that *BRCA2* genetic testing be offered to men with both a personal and family history of PCa, even in the absence of other *BRCA*-related tumor types. However, it is not clear that the overall body of evidence supports this recommendation. The decision not to include Gleason 7 in the criteria proposed here was to avoid making the catchment too broad. Of the 241,000 cases of PCa diagnosed in the United States every year, most are Gleason 6 and below, and Gleason 7 alone constitutes 36% of cases. Gleason 8-10 constitutes 13% of cases, i.e. around 31,330. There are approximately 2,400 genetic health professionals in the United States, totaling more than one million patient care visits per year (www.nsgc.com).

(85) Even if all men with Gleason 8-10 PCa nationwide were referred for genetic counseling, that would represent an additional 13 genetic counseling visits per year for each professional. Of course genetic counseling and testing can also be provided by physicians with experience in cancer genetics. However, given considerations of positive predictive value for combinations of risk factors, it seems prudent to require two risk factors to identify the estimated 3626 men with PCa in the U.S. who carry *BRCA2* mutations.

## 8. GENETIC COUNSELING AND TESTING FOR BRCA MUTATIONS

### 8.1. Benefits of genetic counseling

Professional organizations recommend that genetic testing be provided in the context of genetic counseling by a qualified professional. (35, 38, 86-88) Counseling plays an integral role in the care of patients with suspected mutations. Counselors collect medical and family history, determine eligibility for testing, select appropriate test(s), educate patients, interpret results, and make recommendations about medical management to the patients' providers. As germline tests have traditionally been considered elective, a detailed pretest discussion is considered appropriate to facilitate patient decision-making. Informed consent is legally mandated in some states. (89, 90) The basic elements of informed consent include a discussion of the benefits, accuracy, limitations, and cost of testing; the implications of positive, negative, and uncertain results to the patient and his relatives; medical management options; and a discussion of psychosocial concerns including risks for discrimination in areas such as employment and health insurance, based on results of genetic testing. If the patient and his counselor agree to proceed with testing, written consent is obtained and genetic testing is ordered. A plan for multiple sequential tests is often appropriate. For example, individuals of a specific ethnicity may be tested for founder mutations first, followed by full sequencing (91) and/or large rearrangement testing (92) of the *BRCA1/2* genes, if the family history warrants and the cost is covered. Posttest genetic counseling involves communication of test results and discussion of their implications. If a deleterious mutation is identified, recommendations for medical management and referrals to specialized providers for ongoing screening are made, as outlined in the following section. Negative results and missense variants with unknown clinical implications must be interpreted in the context of the family history, to assess for the possibility of an occult mutation or even a different cancer predisposition syndrome. (93) The family history is used to guide personalized screening and risk-reduction recommendations for the patient and his close relatives. Other family members may be identified for genetic testing to "inform" a proband's negative result, or to explore the segregation of a variant with cancers in that family. Such testing of relatives may significantly alter medical management recommendations for the patient and his offspring. The process of genetic counseling (94-96) and ethical issues (90, 97-100) surrounding genetic testing have been reviewed in more detail elsewhere. (87)

### 8.2. Psychosocial ramifications

Individual reactions to genetic test results vary, and can be significant. Being a member of a family with high rates of cancer poses unique psychosocial challenges, including coping with the attendant fear and anxiety.(101-105) Adequate preparation before testing may promote a smoother adjustment to potentially upsetting results.(106) Referrals can be made for professional psychological support or dedicated support groups.

### 8.3. Management of Male BRCA Carriers

There are benefits to identifying *BRCA* mutations, even in men who already have PCa. Male carriers may be eligible for clinical trials using targeted therapeutics, especially PARP inhibitors (PARPi). (41, 107-109) Providers and patients may search for open trials on the NCI website ([www.nci.gov](http://www.nci.gov)). The higher level of concern for a more aggressive cancer phenotype in carriers may also assist men in nuanced decision-making surrounding treatment and follow-up care.

Positive test results regarding a *BRCA2* mutation alerts men and their providers about their increased risk of developing cancers in other organs. (52) Male carriers have a 5%–10% lifetime risk of male breast cancer, (52) of which they may not otherwise be aware. These men should monitor their breast tissue and seek clinical examination annually. In men with gynecomastia or sufficient breast tissue, annual mammography or sonography may be considered. Carriers of *BRCA* mutations also appear to have an increased risk of pancreatic cancer.(110-114) While there is no formally established screening method for this cancer, concerned patients may consider participation in investigational pancreatic cancer screening programs at large academic centers.(115, 116) Some investigators have reported increased colon cancer risk (110, 117-119) in these families, while others have reported finding no association.(68, 120) Regardless, genetic counseling in this area also provides an opportunity to encourage eligible patients to follow screening recommendation for colonoscopy (every 5 to 10 years over age 50). Similarly, mixed results have been reported regarding the risk of cutaneous melanoma, (114, 121) ocular melanoma, (112) and basal cell carcinoma (122) in mutation carriers. (117) Referrals can be made for dermatologic examination as appropriate. Some authors have suggested increased risks for other cancer types as well, such as gallbladder and bile duct,(114) esophageal and stomach cancer,(110, 112, 114, 117) and lymphoma,(118) although these findings are more controversial. Current research is examining the role of modifier genes (123-125) in more precisely determining individuals' cancer risks. Finally, identification of at-risk individuals will further research in cancer prevention and early detection going forward.

### 8.4. Family Members

A key reason to identify male candidates for *BRCA* testing is to alert their at-risk relatives, especially adult daughters, sisters, nieces, and cousins. Testing will optimally begin with the individual at highest risk for a mutation. If no living family members with breast or ovarian cancer are available and willing to be tested, a male

relative with PCa may be most appropriate. If no mutation is identified, the individual's children may be saved the cost and anxiety of genetic testing. If a mutation is identified, specific at-risk family members can be identified in the follow-up counseling session, and the patient is encouraged to communicate his results to these relatives.(126) Possible barriers to communication, such as feelings of guilt, reluctance to worry family members, (46) and misunderstandings about the implications of test results, can be anticipated and addressed. Relatives may then be offered predictive testing for the specific family mutation. This approach is more cost-effective and more informative than performing full gene sequencing on the family members themselves.

Female carriers of a *BRCA* mutation have between 26% and 87% lifetime risk of breast cancer and 11%–60% lifetime risk of ovarian cancer,(61, 114, 119, 127-135) even if these cancers have not yet occurred in their close relatives. In the absence of testing of the male proband, these women may not otherwise be identified or motivated to test. Women already affected with breast cancer have an increased contralateral breast cancer risk.(114) They can benefit greatly from enhanced breast cancer surveillance beginning from an early age (25–30 years), including breast MRI, (136-142) chemopreventive measures, or even prophylactic breast surgery.(141, 143) Ovarian cancer screening may be offered between ages 30 and 40,(144) and if a mutation is discovered it should be addressed with risk-reducing bilateral salpingo-oophorectomy.(145-147) This is now an outpatient procedure, performed laparoscopically at many centers. Meta-analysis of studies has suggested an 80% reduction in ovarian/fallopian tube cancer risk and a 50% reduction in breast cancer risk.(148) Unaffected male carriers may be offered PCa screening, (i.e., PSA screening and, in some studies, blind prostate biopsy) ideally in the context of a clinical trial such as IMPACT.(149) The age at which to begin screening remains unclear, as there is no evidence of substantial risk before the age of 50, a typical age for starting PCa screening in Caucasian populations. Male and female relatives of *BRCA* mutation carriers who carry these mutations may also be offered screening for pancreatic, colon, skin, and breast cancer as outlined above.

A less obvious use for *BRCA* testing in family members is to inform reproductive decision-making. Both male and female carriers have a 50% chance of passing their mutation along to each child. If the specific mutation is known, couples may wish to meet with a fertility specialist to consider preimplantation diagnosis (PGD). (150, 151) PGD, where feasible, allows for selection of embryos without the mutation to avoid passing the cancer risks to the next generation. (150)

## 9. FUTURE DIRECTIONS

Genetics professionals will need to keep apprised of new clinical tests as they become available in this highly dynamic field. For example, clinical testing of newly identified genes associated with hereditary PCa, such as *HOXB13*, (3, 152, 153) may be offered to *BRCA*-

negative patients. Families may also be considered for genetics research protocols, such as those investigating new cancer predisposition genes or genetic risk-factors. As newer testing methodologies become available, multiplex genetic testing, modifier gene testing, or genomic testing may be offered to patients to more precisely define risks and personalize interventions.

In societal terms, it seems prudent to aim to increase identification of male *BRCA* mutation carriers, through provider awareness and modification of existing guidelines. A longer-term goal would be to identify and counsel all *BRCA1* and *BRCA2* mutation carriers. Reliance on patients' family history will not be adequate to accomplish this latter goal, since not all carriers meet existing family history criteria. (69) With the advent of routine sequencing of tumors in clinical oncology, there is the inherent potential to reveal underlying germline susceptibilities, such as germline mutations in *BRCA1* and *BRCA2* not otherwise ascertained by the current referral criteria. Germline *BRCA* mutation carriers identified in this way will require genetic risk assessment and counseling for their personal and family risk for cancer. It is not known how many individuals will have *bona fide* germline mutations; variants of unknown significance in the *BRCA1* and *BRCA2* genes already provide a significant challenge for genetic counseling. Therefore, additional research will need to focus on more precisely determining individual carriers' cancer risks based on specific family history, mode of ascertainment, and evaluating methods for early detection and prevention. With widespread tumor sequencing and the increased identification of potential germline susceptibility variants, it will be essential to establish higher through-put systems for counseling (154) and medical management of carrying cancer-predisposing mutations.

## 10. AKNOWLEDGMENTS

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