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BRCA1, BRCA2, and Associated Cancer Risks and Management for Male Patients
A Review

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IMPORTANCE Half of all carriers of inherited cancer-predisposing variants in *BRCA1* and *BRCA2* are male, but the implications for their health are underrecognized compared to female individuals. Germline variants in *BRCA1* and *BRCA2* (also known as pathogenic or likely pathogenic variants, referred to here as *BRCA1/2* PVs) are well known to significantly increase the risk of breast and ovarian cancers in female carriers, and knowledge of *BRCA1/2* PVs informs established cancer screening and options for risk reduction. While risks to male carriers of *BRCA1/2* PVs are less characterized, there is convincing evidence of increased risk for prostate cancer, pancreatic cancer, and breast cancer in males. There has also been a rapid expansion of US Food and Drug Administration–approved targeted cancer therapies, including poly ADP ribose polymerase (PARP) inhibitors, for breast, pancreatic, and prostate cancers associated with *BRCA1/2* PVs.

OBSERVATIONS This narrative review summarized the data that inform cancer risks, targeted cancer therapy options, and guidelines for early cancer detection. It also highlighted areas of emerging research and clinical trial opportunities for male *BRCA1/2* PV carriers. These developments, along with the continued relevance to family cancer risk and reproductive options, have informed changes to guideline recommendations for genetic testing and strengthened the case for increased genetic testing for males.

CONCLUSIONS AND RELEVANCE Despite increasing clinical actionability for male carriers of *BRCA1/2* PVs, far fewer males than female individuals undergo cancer genetic testing. Oncologists, internists, and primary care clinicians should be vigilant about offering appropriate genetic testing to males. Identifying more male carriers of *BRCA1/2* PVs will maximize opportunities for cancer early detection, targeted risk management, and cancer treatment for males, along with facilitating opportunities for risk reduction and prevention in their family members, thereby decreasing the burden of hereditary cancer.

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In the 1990s, inherited (ie, germline) loss-of-function variants in *BRCA1* or *BRCA2* (interpreted as pathogenic or likely pathogenic variants by the American College of Medical Genetics, and henceforth referred to as *BRCA1/2* PVs)[1] were linked to familial predisposition to early-onset breast and ovarian cancers.[2-4] In the ensuing decades, studies demonstrated the clinical utility of early detection and risk reduction strategies for breast and ovarian cancer in female carriers of *BRCA1/2* PVs. Within this population, there is a substantial mortality benefit and risk reduction of breast and ovarian cancers through salpingo-oophorectomy.[5] Moreover, poly ADP ribose polymerase (PARP) inhibitors confer mortality benefits in patients with high-risk, early breast cancer and advanced ovarian cancer.[6-9] These findings have led to robust clinical guidelines for female carriers of *BRCA1/2* PVs, although challenges remain in improving genetic testing and ensuring equitable access for carrying out management recommendations.[10]

A widely overlooked group of individuals are male carriers of *BRCA1/2* PVs who are also at increased risk of developing cancer, particularly of the prostate, pancreas, and breast. Males represent half of *BRCA1/2* PV carriers, but most people (including their clinicians) are unaware of their carrier status, associated cancer risks, and management recommendations, or the availability of research opportunities. The population prevalence of *BRCA1/2* PV carriers is roughly estimated at approximately 1 in 250 with variance depending on specific ancestries.[11] The proportion with/without cancer is unknown because males have undergone cancer-specific genetic testing at one-tenth the frequency of female individuals (rate ratio, 0.10 [95% CI, 0.05-0.23]).[12] Patients with prostate cancer, the most common of the

cancers linked with increased risk, have been far less likely to undergo genetic testing (1%) compared to patients with breast and ovarian cancer (52.3%).[13] These differences have been attributed to a variety of causes including lack of inclusion in national guidelines (eg, by the US Preventive Services Task Force), less education and outreach, underrepresentation in studies of informational needs in families, and broader sex differences in health-seeking behaviors.[14-19]

Based on emerging cancer-specific risk estimates in male carriers of *BRCA1/2* PVs along with treatment implications, key professional societies have updated their guidelines.[20,21] However, locating these guidelines is cumbersome as they are in disparate places and buried within guidelines for female carriers, organ-site–specific guidelines, or cancer-focused guidelines. We sought to address this by compiling a comprehensive reference.

In this review, males refer to individuals assigned male sex at birth, regardless of gender identity. While limited evidence suggests that hormonal therapies used by transgender women may affect cancer risk, at present transgender women and gender-neutral/gender-fluid carriers of *BRCA1/2* PVs are recommended to undergo individualized cancer screening based on sex-specific organs.[22]

Discussion and Observations

Appropriate Testing and Identification of Males With *BRCA1/2* PVs

Family History Indications for Genetic Testing

Males unaffected by cancer may meet the criteria for genetic testing if they have 1 or more blood relatives affected by a qualifying cancer or if they meet other criteria (**Box**). It is important to collect family history on both maternal and paternal sides of the family and to inquire broadly about cancer types including breast, ovary, prostate, and pancreas, and if known, approximate age at diagnosis and whether the cancer was lethal. Certain cancer subtypes, such as acinar pancreatic cancer and triple-negative breast cancer, are additional risk factors for hereditary cancer.[23,24] These considerations apply to patients of all ancestries, not only to those for which risks are increased due to *BRCA1/2* PVs that have been better characterized (eg, European or Ashkenazi Jewish). Inquiring about any known familial cancer risk genes is also important.

Personal Cancer History Indications for Genetic Testing

A thorough family history of cancer is necessary but not sufficient for identifying some carriers of *BRCA1/2* PVs. Genetic testing criteria have been in evolution over the last 25 years, and genetic testing is now clinically indicated for males with a personal diagnosis of pancreas adenocarcinoma, breast cancer, or prostate cancer that qualifies as high-risk or very high-risk localized disease based on National Cancer Center Network classification (defined as prostate-specific antigen [PSA] > 20 ng/mL [to convert ng/mL to µg/L, multiply by 1]), Gleason grade 8-10, World Health Organization grade group 4-5), node-positive cancer, or metastatic disease.[20,25] These changes have resulted from studies identifying a high prevalence of *BRCA1/2* PVs among patients with triple-negative breast, ovarian, pancreatic, and aggressive prostate cancer.[26,27] There are also expanding indications for PARP inhibitors, a class of targeted cancer therapies, for patients with ovarian, breast, pancreatic, and prostate cancers who carry *BRCA1/2* PVs.[6-8,28,29]

Box. Clinical Indications for Genetic Counseling and Testing for *BRCA1/2* Pathogenic Variant in Males[a]

Personal History of Cancer Criteria[b]
- Male breast cancer
- Pancreatic cancer
- Prostate cancer that is high risk localized (≥cT3a, Gleason sum ≥ 8, Gleason grade group ≥ 4, prostate-specific antigen ≥ 20 ng/mL[c]), lymph node positive, or metastatic[d]

Family History of Cancer Criteria
- There is a familial *BRCA1/2* pathogenic variant
- There is a family history of any male breast cancer, any pancreatic cancer, or prostate cancer that is high risk localized (cT3a, Gleason sum ≥ 8, Gleason grade group ≥ 4, prostate-specific antigen ≥ 20 ng/mL[c]), node positive, or metastatic[d]
- There is a family history of early (diagnosed before 50 y of age) or triple-negative breast cancer, multiple primary breast cancers, and/or a history of ovarian cancer in close female relatives (first- or second-degree relatives)
- There is a family history of exocrine pancreatic cancer in a first-degree relative
- The family is of Ashkenazi Jewish ancestry

[a] These reflect the minimum criteria for considering genetic counseling and testing for *BRCA1/2* pathogenic variants and should not be considered comprehensive criteria for all cancer predisposition testing. Recommend a genetic counseling referral if there are questions.

[b] Any personal history is sufficient without needing additional family history criteria.

[c] To convert ng/mL to µg/L, multiply by 1.

[d] National Comprehensive Cancer Network risk group criteria.

Published findings on the prevalence of genetic PVs in prostate, pancreatic, and male breast cancers gleaned from historic studies (before broader cancer-directed genetic testing) should be viewed with caution as testing criteria at the time relied exclusively on family history of breast/ovarian cancer without accounting for prostate, pancreatic, male breast, or other cancers. Another major limitation is that current data are largely derived from cohorts that are overwhelmingly of European ancestry or enriched for males of Ashkenazi Jewish ancestry, resulting in a lack of genetic diversity.[30]

Other Indications for Genetic Testing

Many cancer survivors may not have been eligible for genetic testing at the time of their cancer diagnosis and treatment but meet current eligibility criteria and should be offered testing. In addition, genetic testing performed more than a decade ago may have missed *BRCA1/2* PVs identifiable on current tests. Finally, an increasing number of male *BRCA1/2* PV carriers may be identified outside of traditional diagnostic pathways; for example, through prenatal testing, direct-to-consumer testing, and/or matched tumor-normal genetic testing after a cancer diagnosis. Indeed, multiple studies have reported that tumor sequencing can identify germline findings that would be missed by family history criteria.[31-33]

Options for Genetic Testing

There are now increasing options for people to undergo genetic testing; in some cases, patients have sought testing, or testing can be initiated by a primary care clinician or subspecialist, with support from

Table 1. Published Cumulative Cancer Risk Estimates for Male *BRCA1/2* PV Carriers

Cancer type and age		*BRCA2*		*BRCA1*	
Prostate cancer	Age, y	Nyberg et al[40]	Li et al[41]	Nyberg et al[40]	
	50	5.0 (2.0-14.0)	0.2 (0.2-0.3)	4.0 (0.9-13.0)	
	60	10.0 (5.0-21.0)	3.0 (2.0-4.0)	10.0 (5.0-20.0)	
	70	27.0 (17.0-41.0)	13.0 (9.0-17.0)	21.0 (13.0-34.0)	
	80	60.0 (43.0-78.0)	27.0 (21.0-35.0)	29.0 (17.0-45.0)	
Pancreatic cancer	Age, y	Li et al[41]	van Asperen et al[42]	Li et al[41]	
	50	0.2 (0.1-0.3)	0.3 (0-1.0)	0.1 (<0.1-0.2)	
	60	0.9 (0.5-1.4)	1.0 (0-3.0)	0.4 (0.3-0.7)	
	70	2.0 (1.0-3.0)	4.0 (1.0-7.0)	1.0 (0.8-2.0)	
	80	3.0 (2.0-5.0)	7.0 (4.0-10.0)	3.0 (2.0-5.0)	
Male breast cancer	Age, y	Tai et al (2007)[43]	Li et al (2022)[41]	Tai et al (2007)[43]	Li et al (2022)[41]
	30	0.2 (<0.1-0.9)	NA	<0.1 (<0.1-0.1)	NA
	40	1.0 (0.3-4.0)	NA	0.1 (<0.1-0.6)	NA
	50	3.0 (1.0-7.0)	0.2 (0.1-0.5)	0.3 (<0.1-1.0)	<0.1 (0-<0.1)
	60	5.0 (2.0-10.0)	0.7 (0.4-1.5)	0.6 (0.1-ND)	<0.1 (<0.1-0.3)
	70	7.0 (3.0-12.0)	2.0 (1.0-4.0)	1.0 (0.2-3.0)	0.2 (<0.1-0.7)
	80	8.0 (4.0-15.0)	4.0 (2.0-8.0)	2.0 (0.3-5.0)	0.4 (<0.1-1.5)

Abbreviations: NA, not applicable; PV, pathogenic variant.

genetic counselors and other cancer genetics experts. The current genetic counseling workforce cannot meet the demand for their services in most clinical settings, and there is active research investigating new strategies for genetic care delivery through new technologies to improve access and reduce disparities.[34-36] The variation in resources between clinical practice settings will require individualized workflows that can accommodate different patient needs: additional pretest counseling, posttest counseling after identification of PVs, and/or assistance with testing relatives (ie, cascade genetic testing). Ideally, genetic testing can identify carriers of *BRCA1/2* PVs before, or soon after, a cancer diagnosis to enable earlier detection of cancers and better treatment outcomes.

Algorithms for Identifying *BRCA1/2* PV Carriers

Given the limitations discussed previously, existing algorithms estimating the risk of carrying a *BRCA1/2* PV that is reliant on a family history of breast and ovarian cancers have less value for males.[37] However, if the model-derived likelihood for carrying a *BRCA1/2* PV is 5% or greater, individuals in the US are recommended for testing, while thresholds may differ in other jurisdictions (eg, higher in Europe).[38,39]

Risk and Management for Males With *BRCA1/2* PVs

Prostate Cancer–Specific Risks and Clinical Recommendations

Male carriers of *BRCA1/2* PVs are at increased risk of developing prostate cancer compared to their noncarrier counterparts, with the risk from *BRCA2* PVs being higher. Carrying a *BRCA1* PV has been estimated to confer up to a 3.8-fold increased risk of prostate cancer, and an absolute lifetime risk of 15% to 45% (**Table 1**).[40-44] From a cohort of known *BRCA1/2* PV carriers, a *BRCA2* PV is estimated to confer a 4.7- to 8.6-fold increased risk of prostate cancer, and an absolute lifetime risk of 60% (95% CI, 43%-78%).[40] A retrospective analysis of families recruited based on a family history of breast and ovarian cancer (Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2*) also estimated an increased risk, albeit with a notably lower absolute lifetime risk of approximately 27% (95% CI, 21%-35%) for *BRCA2* PV carriers (Table 1).[40-44] Studies of metastatic prostate cancer reveal a substantial enrichment for *BRCA1/2* PVs compared to localized prostate cancer and even more compared to healthy controls, indicating a contribution to both prostate tumorigenesis and to metastatic potential.[27,45,46] Taken together, these and other data are the basis for considering males who carry *BRCA1/2* PVs at particularly high risk for aggressive prostate cancer, although precise risk estimates for the general population of *BRCA1/2* PV carriers are limited.

IMPACT (Identification of Men With a Genetic Predisposition to Prostate Cancer: Targeted Screening) is an ongoing international study designed to assess targeted prostate cancer screening for male carriers of *BRCA1/2* PVs compared to noncarriers (NCT00261456).[47] The screening strategy was annual PSA measurement and prostate biopsy for PSA greater than than 3.0 ng/mL. After 4 screening rounds, the positive predictive value for biopsy was higher in *BRCA2* PV carriers vs noncarriers (39% vs 28%), and a significant difference was observed in detecting intermediate- or high-risk disease (77% vs 40%).[47] Similarly, the positive predictive value for biopsy was higher in *BRCA1* PV carriers vs noncarriers (32% vs 20%), although no significant difference was observed in detecting intermediate- or high-risk disease. Longer follow-up is anticipated, and important questions remain, such as whether a PSA level greater than 3.0 ng/mL is the optimal threshold for biopsy for males with *BRCA1/2* PVs at all ages.

Based on the IMPACT results, national/international guidelines recommend male *BRCA2* PV carriers begin PSA screening between the ages of 40 and 45 years, although there is discordance about intervals: annual vs every 2 years (**Table 2**).[20,21,47-51] The considerations for *BRCA1* PV carriers also vary, reflecting the lower level of evidence and lower estimated risk.[20,48,52] To help define better approaches, *BRCA1/2* PV carriers considering prostate cancer screening should be encouraged to do so in the context of a screening clinical trial whenever possible (**Table 3**).[47,53-67]

Pancreatic Cancer–Specific Risks and Clinical Recommendations

Carriers of *BRCA1* PVs have a 1.9-fold increased risk of pancreatic cancer compared to the general population, with a lifetime risk of pan-

creatic cancer of 3%.[41] Carriers of *BRCA2* PVs have a 3.0- to 7.8-fold increased risk of developing pancreatic cancer, and a lifetime risk of up to 7%.[41,42,68] Importantly, the excess risk of pancreatic cancer in carriers of *BRCA1/2* PVs increases significantly after 50 years of age. Given the substantial morbidity and mortality associated with pancreatic cancer, pancreas screening programs have been developed for *BRCA1/2* PV carriers.

Many professional society guidelines suggest that pancreatic cancer screening for *BRCA1/2* PV carriers can be initiated at 50 years of age, or 10 years prior to the youngest age of pancreatic cancer diagnosis in the family, although there is a lack of consensus on the specifics of screening (Table 2).[20,21,47-51,69] Most guidelines recommend offering screening only to individuals with pancreatic cancer in a close relative from the side of the family with the *BRCA1/2* PV.[20,21,50,51] How family history of pancreatic cancer impacts pancreatic cancer risk for *BRCA1/2* PV carriers remains uncertain,[68] and basing eligibility for screening on family history has limitations, especially when family history is unknown, family size is small, and

Table 2. Guideline-Recommended Management for Male *BRCA1/2* Pathogenic Variant (PV) Carriers[a]

Cancer	Society/panel	Screening recommendations	Concordance between guidelines	Discordance between guidelines
Prostate	NCCN[20]	Recommends annual screening for carriers of *BRCA2* PV with a PSA blood test starting at age 40 y. Consider annual screening for carriers of *BRCA1* PV with a PSA blood test starting at age 40 y.	All societies/panels recommend carriers of *BRCA2* PV be offered screening with PSA blood test, starting at age 40-45 y.	*BRCA2* PV vs *BRCA1* PV: NCCN and ESMO both recommend screening in carriers of *BRCA2* PV. ESMO does not include carriers of *BRCA1* PV in recommendation, while NCCN offers a weaker recommendation to be considered for carriers of *BRCA1* PV. The AUA/SUO guidelines do not make a distinction between carriers of *BRCA1* PV vs *BRCA2* PV. PSA screening interval: AUA/SUO recommends screening every 2-4 y, in contrast to yearly screening recommended by NCCN and ESMO.
	ESMO[21]	Screening should be offered to carriers of *BRCA2* PV with annual PSA blood tests starting at age 40 y.		
	AUA/SUO[48]	Screening should be offered to carriers of *BRCA1/2* PV with PSA blood test starting at age 40-45 y every 2-4 y.		
Pancreatic	NCCN[20]	Screening may be considered in carriers of *BRCA1/2* PV who also have a first- or second-degree relative with a history of pancreatic cancer, starting at age 50 y, or 10 y before the earliest known pancreatic cancer in the family. Screening may be performed with contrast-enhanced abdominal MRI and/or endoscopic ultrasonography.	All societies/panels recommended consideration of screening for pancreatic cancer in eligible carriers of *BRCA1/2* PV starting at age 50 y, or 10 y before the earliest known pancreatic cancer in the family. All societies/panels recommended contrast-enhanced abdominal MRI and/or endoscopic ultrasonography as screening modalities.	Family history of pancreatic cancer: Both NCCN and ESMO restrict recommendations to individuals who carry a *BRCA1/2* PV and also have a first- or second-degree relative with a history of pancreatic cancer. CAPS consortium and AGA are restricted to individuals who carry a *BRCA1/2* PV and also have a first-degree relative with a history of pancreatic cancer. ASGE does not distinguish based on family history of pancreatic cancer among carriers of *BRCA1/2* PV. Measures of pancreatic function: CAPS consortium also recommends a yearly assessment of insulin resistance with either HbA_{1c} and/or fasting blood glucose.
	ESMO[21]	Screening may be considered in carriers of *BRCA1/2* PV who also have a first- or second-degree relative with a history of pancreatic cancer, starting at age 50 y, or 5-10 y before the earliest known pancreatic cancer in the family. Screening may be performed with contrast-enhanced abdominal MRI and/or endoscopic ultrasonography. Recommend screening be carried out as part of a clinical trial.		
	ASGE[49]	Suggests annual screening for carriers of *BRCA1/2* PV at age 50 y, or 10 y before the earliest known pancreatic cancer in the family. Screening may be performed with contrast-enhanced abdominal MRI and/or endoscopic ultrasonography.		
	AGA[50]	Consider annual screening for carriers of *BRCA1/2* PV who also have a first-degree relative with a history of pancreatic cancer, starting at age 50 y, or 10 y before the earliest known pancreatic cancer in the family. Screening may be performed with contrast-enhanced abdominal MRI and/or endoscopic ultrasonography.		
	CAPS consortium[51]	Recommends screening in carriers of *BRCA1/2* PV who also have a first-degree relative with a history of pancreatic cancer, starting at age 45-50 y, or 10 y before the earliest known pancreatic cancer in the family. Screening may be performed with contrast-enhanced abdominal MRI and/or endoscopic ultrasonography as well as fasting blood glucose and/or HbA_{1c}.		

(continued)

Table 2. Guideline-Recommended Management for Male *BRCA1/2* Pathogenic Variant (PV) Carriers[a] (continued)

Cancer	Society/panel	Screening recommendations	Concordance between guidelines	Discordance between guidelines
Breast	NCCN[20]	Breast self-examination training, education, and yearly clinical breast examination starting at age 35 y. Consider annual mammogram at age 50 y or 10 y before the earliest known male breast cancer in the family.	Both societies/panels recommend consideration of screening in male carriers of *BRCA2* PV starting at age 50 y or 10 y before the earliest known male breast cancer in the family. Both societies/panels recommend annual mammogram as an acceptable screening modality. Both societies/panels emphasize patient education and awareness regarding their breast tissue and any changes patients may experience.	*BRCA2* PV vs *BRCA1* PV: NCCN recommends consideration of screening for males who carry *BRCA1/2* PV, though places more emphasis on *BRCA2*, while ESMO solely focuses on *BRCA2*. Additional breast imaging option: ESMO also considers breast ultrasonography as a method of radiologic screening, while NCCN limits screening recommendations to mammography.
	ESMO[21]	In carriers of *BRCA2* PV, consider annual mammogram or at age 50 y or 10 y before the earliest known male breast cancer in the family. Male carriers of *BRCA2* PV should be aware of changes in their breast and seek medical attention when necessary.		

Abbreviations: AGA, American Gastroenterological Association; ASGE, American Society of Gastrointestinal Endoscopy; AUA, American Urological Association; CAPS, International Cancer of the Pancreas Screening; ESMO, European Society of Medical Oncology; HbA_{1c}, glycated hemoglobin; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network PSA, prostate-specific antigen; SUO, Society of Urologic Oncology.

[a] Carriers of *BRCA1/2* PV should be screened for other cancers (eg, colorectal, lung, skin cancers) according to standard population-based and individual risk-based criteria (eg, family history, smoking).

Table 3. Ongoing Cancer Early Detection Clinical Trials in North America for *BRCA1/2* Pathogenic Variant Carriers

Prostate cancer trial (study site)	ClinicalTrials.gov identifier
The IMPACT Study: Identification of Men With a Genetic Predisposition to Prostate Cancer (multisite)[47,53]	NCT00261456
Men at High Genetic Risk for Prostate Cancer (National Cancer Institute)[54]	NCT03805919
Prostate Screening Study Using MRI in *BRCA* Carriers (Toronto Sunnybrook Regional Cancer Centre)[55]	NCT01990521
Prostate Screening for Men With Inherited Risk of Developing Aggressive Prostate Cancer, PATROL Study (multisite)[56]	NCT04472338
Prostate Cancer Genetic Risk Evaluation and Screening Study, PROGRESS (Massachusetts General Hospital)[57]	NCT05129605
MRI Screening in Men at High Risk of Developing Prostate Cancer (University of Chicago)[58]	NCT05608694
Pancreatic cancer trial (study site)	
CAPS5: The Cancer of the Pancreas Screening-5 Study (multisite)[59,60]	NCT02000089
PCEDP: Pancreatic Cancer Early Detection Program (White Plains Hospital)[61]	NCT02206360
Preliminary Evaluation of Screening for Pancreatic Cancer in Patients with Inherited Genetic Risk (University of Pennsylvania)[62]	NCT02478892
A Pancreatic Cancer Screening Study in Hereditary High Risk Individuals (Western Connecticut Health Network)[63]	NCT03250078
PRECEDE: Pancreatic Cancer Early Detection Consortium (multisite)[64]	NCT04970056
Pancreas Scan: Pancreatic Cancer Screening for At-Risk Individuals (multisite)[65]	NCT05006131
Pilot Study of Pancreatic Cancer Screening (University of California, San Francisco)[66]	NCT05058846
A Registry for *BRCA* Mutation Carriers With Pancreatic Ductal Adenocarcinoma (Memorial Sloan Kettering)[67]	NCT05058846

Abbreviation: MRI, magnetic resonance imaging.

when early death from other causes may obscure pancreatic cancer risk.[70,71] Other guidelines advocate for offering pancreatic cancer screening independent of family history.[49]

If pancreatic cancer screening is undertaken, centers have used annual imaging with either endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI) of the abdomen with and without intravenous contrast. Although a recent meta-analysis showed similar performance characteristics for both in the detection of early-stage pancreatic cancer,[72] more recent data suggest EUS may be more effective in identifying solid lesions of the pancreas.[73] The decision to use EUS or MRI for screening in *BRCA1/2* PV carriers is often multifaceted, considering factors such as the need for other endoscopic or imaging procedures (ie, pairing EUS with colonoscopy), anatomic constraints (ie, altered upper gastrointestinal anatomy preventing EUS visualization of the pancreas), local expertise and availability of EUS/MRI, and/or patient preference. Monitoring for the development of new-onset diabetes with annual hemoglobin A_{1C} or fasting glucose can also be considered, because new-onset diabetes may signal developing pancreatic cancer and warrant more attentive screening.[74] However, diabetes monitoring should only be used to complement imaging rather than to replace it. Some studies, but not all, have found pancreatic cancer screening leads to downstaging of screen-detected pancreatic cancer in individuals at high cancer risk and increased long-term survival.[59,75] In the CAPS5 (The Cancer of the Pancreas Screening–5) study, of 1461 individuals screened, invasive pancreatic cancer was detected in 0.7% of individuals.[59]

Importantly, because the goal of pancreatic cancer screening is to identify high-risk pancreatic lesions amenable to curative intent surgical excision, screening should typically only be offered to patients who would be surgical candidates if a high-risk lesion is identified. The risks/costs vs benefits of pancreatic cancer screening should be discussed in-depth prior to embarking on screening, and patients should be counseled that incidental findings in the pancreas, including cysts, are found in approximately one-third of screening participants.[70,76,77] To help define better approaches, *BRCA1/2* PV carriers considering pancreas screening should be encouraged to do so in the context of a screening clinical trial whenever possible (Table 3).[47,53-67]

Breast Cancer–Specific Risks and Clinical Recommendations

While the lifetime incidence of breast cancer is low in males (1 in 833), the risk can be as high as 7% to 9% in male carriers of *BRCA2* PVs.[43,78,79] Male *BRCA1* carriers have an estimated lifetime risk of up to 1.2% of developing breast cancer. There are limited data to

guide breast screening, although data showing younger age of diagnosis, higher tumor grade,[80] increased risk of axillary node-positive disease, and potentially decreased survival in male *BRCA* carriers suggest screening may be of benefit.[43,81,82] National Cancer Center Network guidelines recommend the following: breast awareness and self-examination teaching at 35 years of age, annual clinical breast examinations starting at 35 years of age, and consideration of annual mammogram for *BRCA2* PV carriers starting at 50 years of age, or 10 years before the age of the earliest male breast cancer diagnosis in the family.[20] European Society for Medical Oncology guidelines recommend a similar age to start screening, although allows for either an annual mammogram or ultrasonography.[21] Of note, gynecomastia has not been shown to increase the risk of breast cancer in males and is not a requirement for screening.[20,21] A recent study of male carriers of *BRCA1/2* PVs reported that while breast cancer screening recommendations varied, adherence was 71% (10 of 14) among those who were recommended to undergo screening mammography.[83] Further, screening mammography in males at high breast cancer risk has been shown to yield a similar cancer detection rate in males as in female individuals, suggesting mammography screening may be valuable in male *BRCA* carriers.[84]

Gastric Cancer–Specific Risks and Clinical Recommendations

Studies have demonstrated an excess risk of gastric cancer in carriers of *BRCA1/2* PVs.[41,85,86] Usui et al[86] recently reported a strong interaction between *Helicobacter pylori* infection and *BRCA1/2* PVs, finding that patients with both had a 45% lifetime cumulative risk of gastric cancer, with a greater effect seen in *BRCA2* PV carriers. These studies may be confounded by variance in regional prevalence of *H pylori* and potential misassignment of gastric cancer (vs advanced ovarian cancer). At this time, gastric cancer screening has not been included in formal guidelines, but it may be reasonable to consider baseline *H pylori* testing with a urea breath test or stool antigen assay, especially in areas with high *H pylori* prevalence, and/or if there is a family history of gastric cancer. If a *BRCA1/2* PV carrier opts for pancreatic cancer screening and undergoes EUS, concurrent endoscopic evaluation of gastric mucosa for gastric neoplasia should be considered.[87]

Other Types of Cancer–Specific Risks and Clinical Recommendations

Some cancers have inconsistently been reported to have a modest association with *BRCA1/2* PVs. The observed potential associations may result from ascertainment bias due to increased multigene panel testing in people affected by cancers associated with non-*BRCA1/2* PV cancer syndromes. Although these cancers can occasionally be observed in true association with *BRCA1/2* PVs, the relative risk of *BRCA1/2* PV carriers developing these cancers has not been established to be sufficiently high to support modifying cancer screening due to *BRCA1/2* PVs alone. For example, no studies have shown an increased risk of melanoma or skin cancers with *BRCA1* PVs, and there are conflicting data regarding the risk of *BRCA2* and melanoma along with other skin cancers.[88,89] In a study of cancer types not recognized in association with *BRCA1/2* PVs, melanoma tumorigenesis appeared to be independent of the *BRCA1/2* PV.[89] Thus, it is reasonable to follow population screening guidance and consider annual skin examination if there is a family history of melanoma. For colorectal cancer, studies carried out without ascertainment bias find no increased risk of colon cancer associated with *BRCA1/2* PVs.[90-92] PVs in other genes (eg, Lynch Syndrome) can increase the risk of colon cancer. Therefore, colorectal cancer screening should be considered independent of *BRCA1/2* PV status and be informed by personal and family history—consistent with the American Gastroenterological Association guidelines.[93]

Treatment Implications in Males With Cancer and *BRCA1/2* PVs

An increasing role for genetic testing is the expanding indications for life-prolonging therapies approved for patients with *BRCA1/2* PV–associated cancers, which are sensitive to DNA damage by platinum-based chemotherapy and PARP inhibitors.[94] PARP inhibitors as a class gained initial approval by the US Food and Drug Administration (FDA) for third- and subsequent-line treatment for *BRCA1/2* PV–associated ovarian cancer, followed by maintenance therapy in advanced ovarian cancer, paving the way for subsequent approvals for other *BRCA1/2* PV–associated cancers and in earlier disease settings.[8,9,95-97]

In patients with metastatic castration-resistant prostate cancer, the latest stage of disease, who are carriers of *BRCA1/2* PVs, PARP inhibitors have been shown in phase 3 trials to improve overall survival (olaparib) and progression-free survival (olaparib, rucaparib).[28,29] Additionally, PARP inhibitor and androgen receptor signaling inhibitor combinations (niraparib/abiraterone, talazoparib/enzalutamide, olaparib/abiraterone) have recently been approved by the FDA for biomarker-selected patients with metastatic castration-resistant prostate cancer due to improved radiographic progression-free survival and overall survival.[98-102] Importantly, although platinum chemotherapies are frequently used in ovarian, pancreas, and breast cancers, they have historically had a limited role in prostate cancer; however, they are also an option for patients with advanced prostate cancer and *BRCA1/2* deficiency.[103,104]

For patients with *BRCA1/2* PVs and pancreatic cancer that have not progressed on first-line platinum chemotherapy, a maintenance PARP inhibitor can be considered.[105-107] Retrospective data suggest that patients with pancreatic cancer who carry *BRCA1/2* PVs may have better responses to platinum-based chemotherapy in the first-line setting compared to their noncarrier counterparts.[108,109]

In patients with high-risk breast cancer who carry *BRCA1/2* PVs, adjuvant olaparib has demonstrated disease-free and overall survival benefits among patients with ERBB2-negative disease in the OlympiA trial.[6,7] PARP inhibitors are also FDA approved in the HER2-negative metastatic breast cancer setting based on OlympiAD and EMBRACA.[110-113] Ongoing therapeutic clinical trials are testing the use of PARP inhibitors in earlier cancer settings and in combination with other agents, while also developing novel targeted therapies for patients whose cancers are associated with *BRCA1/2* PVs.

Clinical Trials of Early Cancer Detection

A number of early-detection clinical trials are available for male *BRCA1/2* PV carriers (Table 3).[47,53-67] These trials seek to improve management and optimize screening and risk reduction interventions for people at risk for cancer. Better awareness of available options for tailored management approaches for *BRCA1/2* PV carriers as well as opportunities to explore novel early cancer detection approaches and interception strategies may provide further motivation for males to consider genetic testing.

Other Investigational Screening Strategies

There is keen interest in new technologies that may improve early cancer detection, including novel imaging approaches and minimally invasive circulating biomarkers, eg, from urine and blood. Among these are multicancer early detection tests, which are being developed by commercial companies and academic laboratories. To date, none have established clinical utility for carriers of *BRCA1/2* PVs, and therefore are not included in current recommended guidelines or standard of care. Pending a better understanding of performance characteristics and clinical utility, these tests should be undertaken as part of prospective clinical trials when possible. At most, they should supplement but not replace standard screening tests.

Attention has been given to polygenic risk scores (PRS), which combine common genetic variants found in all individuals (not just those at high risk) into a single continuous variable intended to quantify the genetic risk of cancer. PRS have historically been studied largely in European populations, and noncancer PRS have conflated environmental and social risk factors with biological risk of disease.[114,115] While PRS is being studied for prostate, pancreas, and male breast cancers,[116] there remains no established clinical utility for modified management of *BRCA1/2* PV status based on PRS outside of research trials.

Other Considerations

Additional key considerations for identifying and caring for male carriers of *BRCA1/2* PVs and reviewed elsewhere include genetic testing implementation challenges,[117,118] strategies to overcome barriers to testing and cascade testing,[119] family planning and preimplantation genetic diagnosis considerations, which may motivate testing at an earlier age.[120]

Conclusions

Males who carry *BRCA1/2* PVs are at increased risk for prostate cancer, pancreatic cancer, and breast cancer. Despite the increasing clinical actionability, males are currently much less likely to be offered or complete genetic testing, resulting in lost opportunities to impact health.[15,121] Identifying more male carriers of *BRCA1/2* PVs will maximize opportunities for cancer early detection, targeted risk management, and cancer treatment for males, along with facilitating opportunities for risk reduction and prevention in their family members, thereby decreasing the burden of hereditary cancer.

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