Genetic risk factors for prostate cancer

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INTRODUCTION

Prostate cancer is the most common cancer in males worldwide, with over 1.2 million cases and 358,000 deaths in 2018 according to data from the GLOBOCAN database.

The most important known risk factors for prostate cancer are age, ethnicity, and inherited genetic variants. The genetic risk factors for adenocarcinoma of the prostate are reviewed here. Other risk factors for prostate cancer are discussed separately. (See "Risk factors for prostate cancer".)

HERITABLE FACTORS

Prostate cancer has a strong genetic component. While identification of all genetic contributions to accurately predict individual risk remains challenging, a number of advances have changed clinical practice and research directions.

Evidence supporting the role of genetic factors comes from studies of relatives of patients with prostate cancer (linkage studies), genome-wide association studies, and patients from families with inherited (germline) mutations in known cancer predisposition genes (such as breast cancer susceptibility gene [*BRCA*] 2 and *BRCA1*). Males with germline mutations in *BRCA2*, in particular, are at increased risk of prostate cancer and have more aggressive disease features. In addition, contemporary studies have found a much higher prevalence of known inherited cancer predisposition genes than was previously appreciated in males with more-aggressive-behaving prostate cancer, such as those with early onset, metastatic involvement, and higher

Gleason grade. Together, these observations have led to changes in the recommendations for early detection, diagnosis, and management of prostate cancer in the context of certain pathogenic variants in cancer risk genes.

Defined, heritable (germline) factors contributing to genetic risk can be divided into two main categories:

- Rare deleterious changes, often termed "pathogenic variants" or "mutations," disrupt the function of a known gene. In general, pathogenic variants, such as those in *BRCA2*, are uncommon in the population but are associated with a high lifetime risk of cancer (high penetrance).

- More common variants, often single-nucleotide polymorphisms (SNPs), may be identified within the regulatory or protein-coding regions of a gene or in the intra- or intergenic regions of DNA. These SNPs may directly influence the regulation or function of the gene containing the variant, or the SNP may associate with or regulate a nearby or distant gene that has yet to be directly implicated in the disease. SNPs are relatively common, with allele frequencies of 1 to 5 percent in the population, but they individually confer very modest increases in risk.

These specific inherited factors and the risk of prostate cancer that they confer are discussed in detail below. (See 'Specific genes associated with inherited predisposition' below.)

WHO NEEDS REFERRAL FOR GENETIC EVALUATION

For individuals not yet diagnosed with prostate cancer, a personal and family cancer history (in first- and second-degree relatives), including the type(s) of cancer, age at diagnosis, whether cancer may have contributed to death, and ancestry, may help identify individuals who may carry genetic factors that increase the risk of developing prostate cancer and potentially other cancers. If the family history suggests this possibility, providers should discuss referral to genetic counseling and genetic testing, and shared decision making about genetic testing, as appropriate. For individuals diagnosed with prostate cancer, the personal and family history characteristics described above should be considered, as well as other features, including evidence of metastatic spread and high-risk features in localized cancers, including the presence of intraductal carcinoma (table 1). (See "Interpretation of prostate biopsy", section on 'Intraductal carcinoma of the prostate'.)

Referral to a genetic counseling specialist is important so that patients are educated about basic cancer genetics and inheritance principles, options for genetic testing, and potential

outcomes of testing [1]. In addition, prior to germline genetic testing, minimum pretest education should provide information about the benefits, risks, and limitations of testing, the reproductive and financial implications, and potential further testing of family members (cascade testing). Genetic screening is complex, and the potential benefits should be weighed against the potential negative aspects, including psychosocial consequences, disclosure to family members, and genetic discrimination. (See "Genetic testing" and "Genetic counseling: Family history interpretation and risk assessment".)

Thus, it is strongly recommended that all patients have access to genetics professionals, although with markedly expanded indications for genetic testing, new care delivery models are being explored [2,3]. One such example is mainstreaming, where most or all patients undergo standard pretest education and genetic counselors are triaged to meet with only a subset of patients who may have a very strong family history of cancer; concerns or unanswered questions; and/or who are identified to have a pathogenic variant, likely pathogenic variant, and/or variant of uncertain significance [4]. While there is ongoing debate about optimal care delivery, variable to limited patient access to genetics resources means more research into these models is needed.

Current guidelines from the National Comprehensive Cancer Network (NCCN) on management of prostate cancer and hereditary cancer testing criteria for genetic/familial high-risk assessment of breast, ovarian, and pancreatic cancer recommend that genetic counseling and testing be offered to males with the following [5]:

- Family history of high-risk germline mutations (eg, *BRCA1* and *BRCA2*, Lynch mutation).
- Strong family history of prostate cancer (brother, father, or multiple family members who were diagnosed with prostate cancer [but not clinically localized grade group 1 (table 2)] at less than 60 years of age or who died from prostate cancer).
- Ashkenazi Jewish ancestry.
- Three or more cancers on the same side of the family, especially diagnoses ≤50 years of age: bile duct cancer, colorectal cancer, breast cancer, endometrial cancer, gastric cancer, kidney cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer (but not clinically localized grade group 1), small bowel cancer, or urothelial cancer.
- A personal history of high-grade (Gleason score ≥7) prostate cancer with Ashkenazi Jewish ancestry; one or more close relatives with breast cancer at age ≤50 or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or two or more close relatives with breast or prostate cancer (any grade) at any age.

- A personal history of regional (node-positive) or metastatic prostate cancer, particularly if intraductal or cribriform histology is observed on pathology.

More specific and stringent family history criteria have been suggested which, if available, can further refine the selection of males for genetic testing [6]:

- Three or more affected relatives spanning three generations on the same side.
- Two or more first- and/or second-degree relatives diagnosed with prostate cancer at an age of 55 or younger.

We suggest that clinicians incorporate these factors into decision making for referral for genetic testing, if the information is available and relevant. (See 'Impact of family history' below.)

Two consensus conferences have addressed emerging areas in genetic counseling and genetic testing for prostate cancer: the St. Gallen Advanced Prostate Cancer Consensus Conference 2017 [7] and the Philadelphia Prostate Cancer Consensus Conference 2019 [8]. Both consensus statements endorsed adequate pretest and post-test genetic counseling for males with prostate cancer considering genetic testing. The guidelines from the 2019 Philadelphia consensus conference endorses testing of all males with metastatic prostate cancer as well as those with a family history of cancer suggesting a hereditary predisposition, and suggests using gene panels, with priority given to *BRCA1/2* and DNA mismatch repair genes [8].

Treatment implications — A high frequency of deleterious germline mutations has been found in DNA repair genes in the advanced prostate cancer population. The identification of a germline mutation in *BRCA2* or other DNA repair genes may have implications for treatment in males with metastatic prostate cancer (table 3):

- **Chemotherapy implications** – Patients with metastatic castration-resistant prostate cancer (CRPC) carrying *BRCA2*, *BRCA1*, or ataxia telangiectasia mutated (*ATM*) mutations have similar progression-free and overall survival with both abiraterone and enzalutamide compared with those without such mutations, and outcomes may be better with these two drugs than with taxanes in mutation carriers as well [9,10]. (See "Overview of the treatment of castration-resistant prostate cancer (CRPC)".)

  In addition, significant responses to platinum-based chemotherapy have been reported in metastatic CRPC with *BRCA* mutations. Although most of the data are from single case reports and small retrospective series, clinical trials testing the benefits of platinum agents in males with *BRCA*-mutated metastatic CRPC are underway, and eligible males should be encouraged to enroll. (See "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Platinum-based regimens'.)

- **Utility of PARP inhibitors** – Phase II and III clinical trials of poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors have also demonstrated responses in males with germline or somatic mutations in *BRCA2, BRCA1, ATM, CHEK2, PALB2,* and alterations in other genes that repair DNA by homologous recombination; rucaparib and olaparib have been approved by the US Food and Drug Administration for males with metastatic CRPC harboring these mutations. (See "Management of advanced prostate cancer with germline or somatic homologous recombination repair deficiency".)

- Loss of DNA mismatch repair (Lynch syndrome) may identify males with advanced disease who might be candidates for immune checkpoint inhibitor immunotherapy. (See "Immunotherapy for castration-resistant prostate cancer", section on 'PD-1 pathway inhibition'.)

- Finally, *BRCA2* (and possibly *ATM*) mutations might inform decision making about active surveillance in males with low-risk and intermediate-risk disease [8]. (See "Active surveillance for males with clinically localized prostate cancer", section on 'Other factors'.)

Thus, an emerging group of patients is those undergoing somatic/tumor genomic sequencing for treatment decision making (ie, for treatment and/or clinical trial consideration) whose results suggest the potential for inherited cancer predisposition. Ideally, these patients should be counseled, **prior to** tumor sequencing, about the potential of uncovering germline findings.

Access to genetic counseling specialists is important so that patients may be educated about basic cancer genetics and inheritance principles, options for genetic testing, and potential outcomes of testing. In addition, prior to germline genetic testing, education should provide information about the benefits, risks, and limitations of testing, the reproductive and financial implications, and the potential need for further testing of family members (cascade testing).

SCREENING IMPLICATIONS OF INCREASED GENETIC RISK

For patients with an inherited predisposition to prostate cancer, we advise consultation at a center of excellence and recommend participation in clinical trials testing screening strategies (when possible). If clinical trial participation is not feasible, our approach, which largely follows National Comprehensive Cancer Network (NCCN) guidelines, is outlined in the table (table 4) [11].

Patients who develop prostate cancer in the setting of a germline mutation in *BRCA2* have earlier onset disease, a higher percentage of clinically significant disease at biopsy, and worse prostate cancer outcomes and survival [12-15]; whether the same is true in the setting of

germline mutations in *BRCA1* or other genes involved in homology-directed DNA repair (conferring "*BRCA*-ness") is less clear but suspected [15,16]. Males diagnosed with Lynch syndrome involving mismatch DNA repair deficiency also appear to be at an increased risk of developing prostate cancer [17-19]. (See 'BRCA2 and BRCA1' below and 'Lynch syndrome and mismatch repair deficiency' below.)

These data provide the rationale for considering males who carry mutations in cancer predisposition genes as a group at particularly high risk of developing aggressive prostate cancer and who, therefore, may benefit from prostate cancer screening.

Not all genes involved in DNA repair and not all mutations in a given gene are expected to confer the same level of risk for the development of prostate cancer. To date, the most mature data are available for *BRCA2* with respect to lifetime risk for the development of prostate cancer, as well as adverse outcomes associated with a mutation. For other genes, limited information is available, and consequently, pragmatic recommendations for screening and treatment should be considered pending further studies and a stronger evidence base.

IMPACT study — The Identification of Men with a Genetic Predisposition to Prostate Cancer (IMPACT) study (NCT00261456) was established in 2005 to assess targeted PSA screening in males with *BRCA1* or *BRCA2* pathogenic variants; the protocol was extended in 2012 to include males with germline *MLH1*, *MSH2*, and *MSH6* pathogenic variants.

- **Males with germline *BRCA1* and *BRCA2* pathogenic variants** – Interim results are available from the IMPACT protocol which addressed the feasibility and role of prostate-specific antigen (PSA) screening in males aged 40 to 69 years of age who are carriers of germline pathogenic variants in either *BRCA1* or *BRCA2* [15,20]. The updated interim results of the study included 1821 males who carry pathogenic mutations in either *BRCA1* or *BRCA2*, as well as 1206 controls who tested negative for pathogenic *BRCA* mutation in their family [15]. The mean age at study enrollment was 54 years.

  Males were referred for consideration of biopsy based on the criterion of a PSA ≥3 ng/mL. After four rounds of screening, 63 percent (332) had undergone biopsy. Prostate cancer was detected in 112 cases (3.8 percent of the entire cohort). The positive predictive value for detecting cancer with a PSA >3 ng/mL was higher for *BRCA2* carriers than for controls (31 versus 18 percent) and was higher for *BRCA1* carriers than for controls (23 versus 15 percent). The cancer incidence rate per 1000 person-years was higher in *BRCA2* carriers than in noncarriers (19.4 versus 12.0 percent, p = 0.03); *BRCA2* carriers were diagnosed at a younger age (61 versus 64 years, p = 0.04) and were more likely to have clinically significant disease than *BRCA2* noncarriers (77 versus 40 percent, p = 0.01).

- **Males with germline pathogenic variants in *MSH2* and *MSH6* mismatch repair genes** – Early results are also available from the cohort of males with germline *MLH1*, *MSH2*, and *MSH6* pathogenic variants [19]. The interim results included 644 males who carry pathogenic variants in *MLH1* (n = 203), *MSH2* (n = 303), and *MSH6* (n = 134), as well as 184 age-matched controls who tested negative for germline mismatch repair enzyme pathogenic variants in their family, and 134 age-matched noncarrier controls from the *BRCA* cohort, who were added to boost the sample size [15]. The entire cohort totaled 962 individuals. The mean age at study enrollment was 53 years. Within the first screening round, 56 males had a PSA level >3 ng/mL, and 35 biopsies were performed. The incidence of prostate cancer overall was 1.9 percent (18 of 962). Compared with noncarrier controls, prostate cancer incidence was higher among pathogenic variant carriers of *MSH2* (4.3 versus 0.5 percent, p = 0.011), and *MSH6* (3 versus 0 percent, p = 0.034), but no cases were detected in 203 *MLH1* carriers. Notably, the incidence of clinically significant prostate cancer in *MSH2* and *MSH6* carriers was higher compared with noncarrier controls. The mean age at diagnosis in the *MSH2* carriers was 58 compared with 66 years in the noncarriers; for the *MSH6* carriers, the mean age at diagnosis was 63 years. Carriers of *MLH1* mutations were not found to have an increased frequency of prostate cancer and further years of follow-up are planned to ascertain whether *MLH1* mutations are associated with an increased risk of prostate cancer.

  These findings support the use of targeted PSA screening in males with Lynch syndrome and *MSH2* or *MSH6* germline pathogenic variants to identify those with clinically significant prostate cancer.

Guidelines from expert groups — There is variability in the prostate cancer screening and early detection guidelines for males at increased risk due to family history and/or known inherited pathogenic mutations from many professional societies, including the NCCN (prostate cancer early detection, version 1.2022 [21]) and the American Cancer Society (ACS; 2001, reiterated in 2016) [22,23]. Most guidelines focus primarily on PSA levels to stratify risk, but the data from the Prostate Cancer Prevention Trial (PCPT) that even very low PSA risk thresholds (eg, <0.5 mg/mL) will miss some aggressive cancers [24] may justify considering biopsy regardless of PSA level if there is evidence of abnormality using another measure, such as imaging or digital rectal examination (DRE); this is recommended by the NCCN.

- Guidelines from the NCCN recommend referral to a cancer genetics professional for anyone with a personal or family cancer history of high-risk germline pathogenic variant; they recommend prostate cancer screening for *BRCA2* mutation carriers starting at age 40 years, given that these individuals may have an increased risk of early and potentially

lethal prostate cancers before age 65 years, and that screening be considered at annual rather than every other year intervals [21]. The optimal timing to initiate screening for individuals with known or suspected pathogenic variant in other cancer susceptibility genes, such as *HOXB13*, mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), *ATM* or *BRCA1* is less clear, but it is reasonable to begin shared decision-making about the risks and benefits of prostate cancer screening at age 40 years in carriers of other prostate cancer risk genes.

- ACS guidelines from 2001 state that males at an appreciably higher risk of prostate cancer due to multiple first-degree relatives who were diagnosed with prostate cancer at an early age could begin testing at age 40 years [23]. However, if the PSA is less than 1.0 ng/mL, no additional testing is needed until age 45 years. If the PSA is greater than 1.0 ng/mL but less than 2.5 ng/mL, annual testing is recommended. If the PSA is 2.5 ng/mL or greater, further evaluation with biopsy should be considered. Males at high risk should also be informed about the benefits, limitations, and uncertainties associated with testing for early prostate cancer detection.

- The Philadelphia Prostate Cancer Consensus Conference 2019 recommended (≥75 percent consensus) that *BRCA2* mutation status be factored into prostate cancer screening discussions, with a baseline PSA at age 40 years or 10 years prior to the youngest prostate cancer diagnosed in the family [8]. There was less consensus (50 to 75 percent) that mutation status of other homologous recombination repair deficiency-associated genes (eg, *BRCA1*, *ATM*), homeobox B13 (*HOXB13*), and DNA mismatch repair genes (especially *MSH2* and *ATM*) should be factored into the prostate cancer screening discussion because of less evidence for recommending changes to the standard screening guidelines as compared with *BRCA2* carriers, if a mutation is found.

- On the other hand, the most recent draft prostate cancer screening guidelines from the United States Preventive Services Task Force (USPSTF) recommend that males with a family history of prostate cancer talk to their clinician about the potential benefits and harms of screening, with no additional specific guidelines for those with inherited predisposing mutations, such as *BRCA* mutations [25].

- Similarly, year 2013 American Urological Association (AUA) guidelines, which were reconfirmed in 2018, state that, for males younger than age 55 years at higher than average risk (including those with a family history of metastatic or lethal adenocarcinomas [eg, prostate, male and female breast, ovarian, and pancreatic cancers] that spanned multiple generations, affected multiple first-degree relatives, and developed at younger ages), decisions regarding prostate cancer screening should be individualized [26].

FAMILY STUDIES

Impact of family history — The importance of genetic factors is illustrated by two large contemporary studies that studied the impact of a positive family history on the risk of developing prostate cancer:

- The magnitude of increased risk was illustrated by a study from the Prostate Cancer data Base Sweden (PCBaSe) that compared the risk of prostate cancer in 51,897 males who were brothers of 32,807 index cases [27]. The overall risk of developing prostate cancer for males with one brother with the disease by age 65 years was 14.9 percent, compared with 4.8 percent in those without a brother with prostate cancer, and the risk was 30.3 versus 12.9 percent at age 75 years. When the analysis excluded those with low-risk prostate cancer, there was a similar increased risk.

- Additional evidence comes from a prospective study of 203,000 twin pairs (80,000 monozygotic and 123,000 same-sex dizygotic) from Nordic countries; concordance for cancer in monozygotic and dizygotic twins was 38 and 22 percent, respectively, for prostate cancer [28]. This study estimated that as much as 57 percent of the risk of prostate cancer could be explained by heritable factors.

In addition to affecting the risk of developing prostate cancer, inherited factors may influence prognosis for males who develop prostate cancer. In a Swedish study of 610 males with prostate cancer whose fathers had had prostate cancer, the survival of the sons correlated with that of their fathers [29]. When the fathers survived for five years or more, the hazard ratio for death as a result of prostate cancer (deaths from other causes were censored) in their sons was 0.62 (95% CI 0.41-0.94) compared with those whose fathers had survived fewer than 24 months.

While the evidence for linking family history of prostate and other cancers to a man's risk of getting prostate cancer is robust, more specific definitions of family history may affect risk estimates. In a population-based study from Utah of 36,360 males with prostate cancer, the use of the following criteria rather than simply a family history of three or more prostate cancer affected relatives increased the risk of prostate cancer [6]:

- Three or more affected relatives spanning three generations on the same side.
- Two or more first- and/or second-degree relatives diagnosed with prostate cancer at an age of 55 or younger.

Limitations of this study include a homogeneous population, limited clinical details, and increased levels of screening in males with stronger family histories (despite efforts to control

for this).

Impact of specific genetic variants identified in family studies — Studies designed to identify predisposition genes in families with numerous individuals affected by prostate cancer have reported several DNA variants that are associated with a prostate cancer diagnosis, including *HOXB13*, ribonuclease L (*RNASEL*), macrophage scavenger receptor 1 (*MSR1*), elaC ribonuclease Z 2 (*ELAC2*), neurokinin 3 homeobox 1 (*NKX3-1*), and others.

While variants in these individual genes may be strongly associated with a high risk of prostate cancer within specific families, there is substantial heterogeneity across the population and limited reproducibility between studies. Consequently, no single susceptibility locus has been shown to be responsible for a large proportion of familial prostate cancers. The degree of heterogeneity has prevented the use of these variants to ascertain prostate cancer risk in the population.

Furthermore, variants in these genes have not been shown to be associated with aggressive prostate cancers. Thus, males found to carry these variants may be less likely to benefit from early detection and treatment. Currently, a family history of prostate cancer may be similarly or more informative of risk of prostate cancer than the presence or absence of an individual single-nucleotide polymorphism (SNP) or risk variant.

One example of a gene variant identified in studies of high-risk families is *HOXB13*, a gene that codes for a transcription factor that is important in prostate development. The molecular pathways and implications for the molecular pathogenesis of prostate cancer due to abnormalities in *HOXB13* remain to be identified. (See 'HOXB13' below.)

Population studies and inherited DNA variants — Over the past two decades, a large number of population-based assessments have been conducted to identify germline DNA variants that are associated with the development of prostate cancer.

Genome-wide association studies (GWAS) using panels of genome-spanning SNPs have identified more than 100 loci that are associated with a prostate cancer diagnosis [30-39], including multiple loci in the 8q24 region [30-37] and the 17q region [38,39], as well as in other chromosomes [36,37]. Collectively, these variants are estimated to explain approximately 33 percent of the familial risk for prostate cancer.

Additional studies have focused on identifying variants specifically associated with aggressive prostate cancer, including higher Gleason score, cancer recurrence, metastasis, or mortality [40]. However, few such loci have been identified; the relative risks for these variants are low,

generally with an odds ratio of less than 1.3, and have not conferred a sufficient level of risk to warrant routine testing in the population [41].

Ongoing studies are evaluating whether combinations of these common but low-penetrance alleles may collectively indicate a risk level useful for guiding screening or treatment recommendations.

This approach is illustrated by a study that utilized 2893 Swedish males with prostate cancer and 1781 controls. The risk of prostate cancer was evaluated using a panel of five SNPs from three loci in 8q24 as well as single sites in 17q12 and 17q24.3 [39]. Although the increased risk was relatively limited if any one of these SNPs was present (risk ratio 1.22 to 1.53), the risk increased dramatically if four of the five SNPs were present (risk ratio 4.47, 95% CI 2.93-6.80). The risk was further increased if four or five of the SNPs were present and the subject had a family history of prostate cancer in a first-degree relative (risk ratio 9.46, 95% CI 3.62-24.72).

Despite the association of these genetic variants with the development of prostate cancer, none of the five was significantly associated with prognostic parameters in males with prostate cancer (Gleason score, serum prostate-specific antigen [PSA] level at diagnosis, age). Although the information from a panel of these markers may be useful in identifying males who are at increased risk for prostate cancer, additional prospective evaluations are necessary to establish the utility of this approach and whether the presence of individual variants or combinations of these variants (polygenic risk) is associated with adverse outcomes such as metastasis and mortality.

Although an SNP associated with prostate cancer may not reside within a known gene, it can be used to localize candidate genes that require further confirmation. Among the genes that have been suggested in this way are *HOXB13*, microseminoprotein beta (*MSMB*), lemur tyrosine kinase 2 (*LMTK2*), kallikrein-related peptidase 3 (*KLK3*), copine 3 (*CPNE3*), interleukin 16 (*IL16*), cadherin 13 (*CDH13*), and hepatocyte nuclear factor 1B (*HNF1B*) [36,37,42].

Genes identified through GWAS may eventually have a role in prostate cancer screening. Alternatively, given the increasingly appreciated complexity of the noncoding genome, it is also plausible that these SNPs affect the expression of distant genes or the regulation and function of noncoding RNAs in ways that are yet to be fully appreciated.

Limitations in genetic screening should also be noted. Differences in the contributions of various SNPs to prostate cancer risk across races and ethnic groups would not be unexpected. The vast majority of family and population-based studies designed to identify genetic risk variants for prostate cancer have been conducted in White populations, with very limited

studies in other races or ethnic groups [43,44], although a newer study has examined GWAS in cohorts with wider representation of ancestry [45].

The deletion of sequences from chromosome 8p is a common event in the somatic genome of prostate tumors [46]. Results from genetic linkage studies have also provided some evidence that germline 8p alterations may be linked to hereditary prostate cancer [47,48]. Whether there is a connection between germline and somatic genetic changes has yet to be established.

Combining multiple SNPs with PSA may improve predictive power for detecting prostate cancer. The Stockholm 3 (STHLM3) study was a prospective, population-based screening study for males aged 50 to 69 years that combined plasma biomarkers, genetic polymorphisms, and clinical variables with PSA. In this study, the use of a combination of parameters was more effective than PSA alone in detecting Gleason 7 or higher prostate cancer and in reducing 44 percent of unnecessary biopsies [49].

Additional studies are needed in broader populations to determine whether new models and biomarkers can be combined with PSA levels and other clinical factors (ie, age, race, family history, prior biopsies) to identify males who are at particularly high risk for prostate cancer.

SPECIFIC GENES ASSOCIATED WITH INHERITED PREDISPOSITION

DNA repair genes — Germline mutations in genes involved in the process of repairing DNA by homologous recombination are associated with increased rates of developing several malignancies (ie, hereditary breast and ovarian cancer syndrome). These mutations are also associated with Fanconi anemia, an inherited bone marrow failure syndrome characterized by pancytopenia, predisposition to malignancy, and the presence of specific physical abnormalities. (See "Cancer risks in BRCA1/2 carriers" and "Clinical manifestations and diagnosis of Fanconi anemia".)

Detailed genetic and molecular studies of Fanconi anemia have identified mutations in a number of genes that cooperate in repairing DNA by homologous recombination. Members of the Fanconi family of genes, most notably *BRCA2* and *BRCA1*, are associated with hereditary predisposition to breast and ovarian cancer, as well as prostate cancer, pancreatic cancer, and others. An increased risk of prostate cancer for carriers of mutations in *ATM* has been reported, and further investigation is needed to establish the level of increased risk for carriers of mutations in checkpoint kinase 2 (*CHEK2*), partner and localizer of *BRCA2* (*PALB2*), nibrin (*NBN*), and more recently implicated DNA repair genes, such as recombination protein A (*RAD*) 51 and Fanconi anemia complementation group A (*FANCA*).

Distribution — The majority of the genes associated with an inherited predisposition to prostate cancer are *BRCA* genes. The distribution of specific gene variants in males with prostate cancer has been addressed in the following studies:

- One cross-sectional study included 3607 males with a personal history of prostate cancer who were unselected for family history and referred for germline genetic testing over a five-year period (2013 to 2018) [50]. Of the pathogenic or likely pathogenic variants that were identified in this cohort (in 674 males, 24 percent of the total), 164 (24 percent of the mutations) were in *BRCA2*, 95 (14 percent) were in *CHEK2*, 64 (10 percent) were in *ATM*, 58 (8.6 percent) were in one of the mismatch repair genes associated with Lynch syndrome, 43 (6.4 percent) were in *BRCA1*, 30 (4.5 percent) were in *HOXB13*, 17 (2.5 percent) were in *PALB2*, and 10 (1.5 percent) were in *NBN*. The findings included the observation that a substantial proportion of males with germline mutations would not have been recommended to have genetic testing based on earlier versions of the National Comprehensive Cancer Network (NCCN) guidelines, highlighting the importance of the most recent updates to the NCCN guidelines pertaining to which patients should be offered genetic testing. (See 'Who needs referral for genetic evaluation' above.)

- In another study, 7636 unselected Japanese males with prostate cancer and 12,366 male cancer-free controls underwent sequencing for eight genes associated with hereditary prostate cancer (*ATM*, *BRCA1* and *2*, BRCA1-interacting protein c-terminal helicase-1 [*BRIP1*], *CHEK2*, *HOXB13*, *NBN,* and *PALB2*) [51]. Overall, germline pathogenic variants were found in 219 males with prostate cancer (2.9 percent) compared with 99 controls (carrier frequency 0.8 percent). The majority of the germline mutations found in males with prostate cancer were *BRCA2* mutations (83 males, 38 percent of the total), followed by *HOXB13* (61 males, 28 percent of the total), *ATM* (37 males, 17 percent of the total), *BRCA1* (14 males, 6 percent of the total), and *CHEK2* (12 males, 5 percent of the total); *PALB2, BRIP1,* and *NBN* mutations accounted for fewer than 2 percent each. Association with prostate cancer risk was statistically significant for variants in *BRCA2* (odds ratio [OR] 5.65, 95% CI 3.55-9.32), *HOXB13* (OR 4.73, 95% CI 2.84-8.19), and *ATM* (OR 2.86, 95% CI 1.63-5.15).

Aggressive prostate cancer — Because germline mutations in DNA repair genes are relatively rare in the general population, current guidelines for germline testing include evaluation of genetic risk based on a family history of cancer and/or a known germline mutation in a relative. (See 'Who needs referral for genetic evaluation' above.)

However, studies using panel testing and high-throughput sequencing technologies have identified specific subgroups of males with a personal history of prostate cancer who are more likely to carry inherited mutations in DNA repair genes, including those with metastatic disease

and/or who have certain histologic features (ie, intraductal) reported on tumor pathology [52-56]:

- In a study of 692 males with metastatic prostate cancer, germline DNA was analyzed for the presence of mutations in 20 DNA repair genes known to be associated with cancer predisposition syndromes [52]. This cohort was not selected on the basis of either a family history of cancer (including prostate) or age at diagnosis. Mutations were identified in 82 males (11.8 percent). This was significantly more frequent than in a cohort of 499 males with localized prostate cancer (2 percent of males with low- to intermediate-risk cancers and 6 percent of males with high-risk tumors) or in a cohort of 53,105 males without a known cancer diagnosis (2.7 percent). Mutations were identified in 16 of the 20 genes studied. The most commonly involved gene was BRCA2 (37 males, 5.3 percent of those analyzed). Other genes involved included ATM (11 males, 1.6 percent), CHEK2 (10 males, 1.9 percent), BRCA1 (6 males, 0.9 percent), RAD51D (3 males, 0.4 percent), and PALB2 (3 males, 0.4 percent). Mutations were also identified in 11 other DNA repair genes.

- Intraductal carcinoma of the prostate is a distinct histologic entity that represents retrograde spread of invasive acinar adenocarcinoma into prostatic acini and ducts with basal cell preservation. This histologic variant is associated with an aggressive clinical course, including an increased risk of biochemical recurrence, metastasis, and mortality (see "Interpretation of prostate biopsy", section on 'Intraductal carcinoma of the prostate'). Moreover, these histologic features of prostate cancer are also enriched for carrying driver mutations. For example, males with germline *BRCA* mutations are more likely to have intraductal features in their prostate cancer [53,54].

Prognostic impact — Germline mutations in these genes, especially *BRCA2*, are associated with aggressive prostate cancer and worse outcomes. As examples:

- A retrospective study of 799 patients with localized prostate cancer included 313 who died of their disease and 486 with low-risk, localized prostate cancer who did not; germline DNA was sequenced for mutations in BRCA1, BRCA2, and ATM in all 799 cases [14]. The combined incidence of mutation in any of these genes was significantly higher in those with lethal prostate cancer compared with localized disease (6.1 versus 1.4 percent). Furthermore, among those with lethal prostate cancer, the incidence of a mutation in *BRCA1*, *BRCA2*, or *ATM* decreased progressively as a function of age at death (10 percent for those ≤60 years to 3 percent for those >75 years), suggesting that these mutations contribute to an earlier age of death due to prostate cancer.

- A study of 67 *BRCA* carriers and 1235 noncarriers determined that, at 3, 5, and 10 years after treatment, 97, 94, and 84 percent of noncarriers and 90, 72, and 50 percent of carriers were without metastasis (p <0.001). Multivariate analysis identified *BRCA* mutation as an independent prognostic factor for metastasis-free survival (hazard ratio [HR] 2.36, 95% CI 1.38-4.03, p = 0.002) [57].

- The PROREPAIR-B study was a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of males with metastatic castration-resistant prostate cancer (CRPC) [9]. Of the 419 unselected males with newly diagnosed CRPC who were screened for germline mutations in 107 genes at the time of diagnosis, 68 carriers (16 percent) were identified, including 14 with *BRCA2*, eight with *ATM*, and four with *BRCA1*. Although the difference in cause-specific survival between *ATM*/*BRCA2*/*BRCA1* mutation carriers and noncarriers was not statistically significant (23 versus 33 months, p = 0.264), cause-specific survival was significantly less in *BRCA2* carriers (17 versus 33 months).

BRCA2 and BRCA1 — Breast cancer susceptibility gene (*BRCA*) mutations exhibit an autosomal dominant pattern of inheritance, and males found to be carriers of *BRCA* mutations are often identified through the evaluation of families with females diagnosed with breast or ovarian cancer. Information regarding the lifetime risk of developing breast and ovarian cancer in females who carry *BRCA2* and *BRCA1* mutations is sufficiently mature to enable informed counseling regarding screening and risk-reduction strategies. However, corresponding information for prostate cancer risk is limited, but growing.

For *BRCA2* mutation carriers, the relative risk of prostate cancer is estimated to be increased 2.2- to 8.6-fold compared with noncarriers [58-62]. The estimated cumulative incidence of prostate cancer before age 65 years was 7 to 33 percent in one study [63]. Another study reported a range of risk by age 80 years at the 5^{th} and 95^{th} percentile of 19 to 61 percent for *BRCA2* mutation carriers [64].

Retrospective studies determined that *BRCA2* mutation carriers present at a younger age with higher Gleason score tumors, higher rates of lymph node involvement, distant metastasis when diagnosed, and a higher rate of prostate cancer-specific mortality [12,14,57,65-70].

The risk of prostate cancer in males with a *BRCA1* mutation may be increased as much as 3.75-fold although not as high as for *BRCA2* [71]. Others have failed to document a significantly increased risk [61,62]. In the above-mentioned study of *BRCA1* and *BRCA2* mutation carriers, a range of risk by age 80 years was observed at the 5^{th} and 95^{th} percentile of 7 to 26 percent for *BRCA1* mutation carriers [64]. There is also similar evidence that males with *BRCA1* mutations present with more aggressive disease [12,13].

ATM — A study of 104,000 Icelanders that focused on genetic variants associated with gastric cancer identified two monoallelic loss-of-function variants of ataxia telangiectasia mutated (*ATM*) that, in addition to an association with gastric cancer, were also associated with prostate cancer risk (OR 2.18) [72]. Rare biallelic pathogenic variants give rise to ataxia-telangiectasia. (See "Ataxia-telangiectasia".)

HOXB13 — Homeobox B13 (*HOXB13*) is a gene that codes for a transcription factor that is important in prostate development. The molecular pathways and implications for the molecular pathogenesis of prostate cancer due to abnormalities in *HOXB13* remain to be identified. (See "Molecular biology of prostate cancer", section on 'HOXB13'.)

The G84E variant of *HOXB13* was identified by sequencing the 17q21-22 region in four families with pedigrees strongly indicative of hereditary prostate cancer predisposition [73]. The following data are available regarding the link to prostate cancer:

- The original study evaluating 5083 unrelated European subjects with prostate cancer and 1401 controls found a 20-fold increase in the frequency of the *HOXB13* G84E variant in males with prostate cancer compared with those without prostate cancer (1.4 versus 0.1 percent) [73].
- This *HOXB13* G84E variant was identified in 1.1 percent of a cohort of 3607 males with a history of prostate cancer who were referred for germline genetic testing [50].
- A pooled analysis of 25 epidemiologic studies encompassing over 145,000 individuals reported an OR of 3.23 (95% CI 2.3-4.6) for prostate cancer risk in male carriers of a germline *HOXB13* G84E variant [74]. A slightly higher risk for prostate cancer in mutation carriers (OR 4.81, 95% CI 4.06-5.68) was noted in a separate population-based analysis of approximately 500,000 individuals derived from the UK Biobank [75].
- *HOXB13* G84E does not distinguish between those cancers exhibiting indolent features and those with aggressive features [76].

A rare African ancestry-specific germline deletion in HOXB13 has been identified, and associated with a 2.4-fold increase in prostate cancer, with a greater risk for aggressive and advanced disease [77].

Lynch syndrome and mismatch repair deficiency — Lynch syndrome is the most common cause of inherited colorectal cancer. It is characterized by a significantly increased risk of colorectal and endometrial cancer, as well as other malignancies. Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA

mismatch repair genes: mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), mutS homolog 6 (*MSH6*), and postmeiotic segregation increased 2 (*PMS2*). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis".)

Mounting evidence suggests a moderately increased risk of prostate cancer in males with Lynch syndrome, as illustrated by the following reports [18,19,78-80]:

- A systematic review and meta-analysis of 12 reported risk studies concluded that male carriers of Lynch syndrome pathogenic variants in clinic-based retrospective cohort series had a 2.12-fold higher risk of prostate cancer (95% CI 1.45-2.80) relative to noncarriers of the general population, and for males from mutation-carrying families. the risk was 2.28-fold elevated (95% CI 1.37-3.19) [18].

- The Prospective Lynch Syndrome Database (PLSD) reported on 6350 males with a Lynch syndrome gene mutation and 51,646 years of follow-up and found that 1808 were prospectively observed to have cancer; risks were quantified by gene and gender. Of note, *MSH2* carriers were noted to have a higher risk of prostate cancer, especially with increasing age (23.8 percent cumulative incidence of prostate cancer by age 75 years versus 13.8 percent for *MLH1*, 8.9 percent for *MSH6*, and 4.6 percent for *PMS2* by age 75 years) [80].

- As described above, the IMPACT study prospectively assessed PSA screening in males age 40 to 69 years of age with a known germline pathogenic variant in *MLH1*, *MSH2*, or *MSH6*, and compared them with age-matched noncarrier controls [19]. (See 'IMPACT study' above.)

  In the interim analysis after the first round of prostate cancer screening, compared with noncarrier controls, prostate cancer incidence was higher among pathogenic variant carriers of *MSH2* (4.3 versus 0.5 percent, p = 0.011), and *MSH6* (3 versus 0 percent, p = 0.034), but no cases were detected among the 203 *MLH1* carriers.

Collectively, these studies suggest that prostate cancer should be considered for inclusion in the Lynch syndrome tumor spectrum, at least in those with germline *MSH2* and *MSH6* pathogenic variants.

CHEK2 — Checkpoint kinase 2 (*CHEK2*) is involved in the activation of DNA repair in response to double-strand breaks. A pooled analysis of 12 prostate cancer studies found that male germline carriers of the *CHEK2* 1100delC mutation have an increased risk of prostate cancer, particularly if they have a family history of prostate cancer. The pooled ORs were 1.98 (95% CI 1.23-3.18) for unselected cases and 3.39 (95% CI 1.78-6.47) for familial cases [81].

In a study of 87,000 individuals from the Copenhagen General Population Study, there was an age- and sex-adjusted HR of 1.60 (95% CI 1.00-2.56) for prostate cancer in those carrying *CHEK2* 1100delC compared with noncarriers [82].

An international study that included 22,000 prostate cancer cases and 22,000 controls and specifically analyzed *PALB2, CHEK2,* and *ATM* using a genotyping array found an increased risk for *CHEK2* c.1343T>G (OR 3.03, 95% CI 1.53-6.03, p = 0.0006) for African males and *CHEK2* c.1312G>T (OR 2.21, 95% CI 1.06-4.63, p = 0.030) for European males [83].

NBN (also called NBS1) — In a Polish study, the germline nibrin (*NBN*) 657del5 founder mutation was observed in 5 of 56 males with familial prostate cancer (OR compared with controls 16, p = 0.001) and in 7 of 305 nonfamilial prostate cancer cases (OR 3.9 compared with controls, p = 0.01). The germline *NBN* 657del5 mutation was identified in only 9 of 1500 control males without prostate cancer [84].

PALB2 — Germline mutations in partner and localizer of *BRCA2* (*PALB2*) have been implicated in prostate cancer risk due to unselected enrichment in metastatic prostate cancer [52] and reports of loss-of-function mutation segregation within prostate cancer families, such as in a study of Finnish cancer families that identified *PALB2* c.1592delT as a recurrent truncating mutation associated with breast cancer susceptibility and the reported segregation within a prostate cancer family [85]. However, other studies have failed to find an association between *PALB2* mutations and an elevated risk of prostate cancer [86], possibly because of the low prevalence of these mutations in prostate cancer and the inability to distinguish between low-risk (eg, Gleason score 6) and high-risk (eg, Gleason score 8 to 10, metastatic) cancers [50]. (See 'Distribution' above.)

Implications of somatic tumor genomic testing — There is increasing interest in and use of somatic (tumor) genomic sequencing approaches to identify prostate cancers with DNA repair alterations for therapeutic decision making and clinical trial consideration. These assays may use tumor biopsies or circulating tumor DNA sampled from blood. Phase III data have been reported for poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors in males with *BRCA*-mutated tumors, and this has led to approval of two PARP inhibitors (olaparib, rucaparib) for treatment of advanced disease in the setting of germline or somatic mutations in genes that are involved in homologous recombination repair. (See "Management of advanced prostate cancer with germline or somatic homologous recombination repair deficiency", section on 'Castration-resistant disease'.)

Because somatic tumor genomic testing has the potential to identify mutations in inherited cancer predisposition genes, it is important to discuss this possibility with patients and get their

consent prior to tumor testing. In a study of targeted DNA sequencing of tumor and matched normal blood (germline) pairs for 451 patients with locally advanced or metastatic prostate cancer, 27 percent were found to have a somatic mutation and/or a germline pathogenic variant in DNA repair genes, with 19 percent having evidence of germline mutations in genes associated with inherited cancer predisposition [87].

It should be noted that most commercial tests for tumor genomic sequencing are currently limited to reporting tumor-only results and are not validated for germline cancer predisposition testing, although paired somatic/germline testing is becoming more available [88]. When the identification of a cancer-predisposition-associated mutation occurs from tumor (eg, *BRCA2*, *BRCA1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*), providers should be prompted to refer patients to genetic counseling for discussion of dedicated, confirmatory germline genetic testing. In addition, it is important to recognize that the absence of a germline mutation on somatic-only sequencing is not a sufficient substitute for dedicated germline testing. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Prostate cancer screening (Beyond the Basics)")

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis and

management of prostate cancer".)

SUMMARY AND RECOMMENDATIONS

- **Heritable factors and risk assessment**
  - Prostate cancer has a strong inherited component. Having a family history of prostate cancer and/or other potentially heritable cancers (eg, breast cancer diagnosed at age <50 years, male breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, melanoma) may increase the risk of prostate cancer. (See 'Heritable factors' above.)
  - Genetic counseling and testing should be offered to all males with the following:
    - Family history of high-risk germline mutations (eg, breast cancer susceptibility gene [*BRCA] 1* and *BRCA2*, Lynch mutation).
    - Strong family history of prostate cancer (brother, father, or multiple family members who were diagnosed with prostate cancer [but not clinically localized grade group 1 (table 2)] at less than 60 years of age or who died from prostate cancer).
    - Ashkenazi Jewish ancestry.
    - Three or more cancers on the same side of the family, especially diagnoses ≤50 years of age: bile duct cancer, colorectal cancer, breast cancer, endometrial cancer, gastric cancer, kidney cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer (but not clinically localized grade group 1), small bowel cancer, or urothelial cancer.
    - A personal history of high-grade (Gleason score ≥7) prostate cancer with Ashkenazi Jewish ancestry; one or more close relatives with breast cancer at age ≤50 or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or two or more close relatives with breast or prostate cancer (any grade) at any age.
    - A personal history of regional (node-positive) or metastatic prostate cancer, particularly if intraductal or cribriform histology is observed on pathology
  - Genetic risk assessment should include a detailed personal and family cancer history (in first- and second-degree relatives), including the type of cancer, grade and stage (if available), age at diagnosis, and ancestry. If the family history is suggestive, patients

should be referred for genetic counseling and genetic testing, as appropriate (table 1). Pretest genetic education should include a discussion of the risks and benefits of genetic testing, test choice, results interpretation, management changes, and relevant follow-up for patients and family members. (See 'Who needs referral for genetic evaluation' above.)

- Relatively rare germline variants/mutations in some genes increase the risk and aggressiveness of prostate cancer. These genetic factors (particularly *BRCA2* and *BRCA1 m*utations) may also suggest additional management changes in cancer screening and treatment decision making (table 3). (See 'Specific genes associated with inherited predisposition' above and 'Treatment implications' above.)

- Tumor/somatic genomic testing (which may be undertaken for treatment decision making and clinical trials consideration) may identify mutations in known cancer predisposition genes (such as *BRCA2*, *BRCA1*, mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], mutS homolog 6 [*MSH6*], postmeiotic segregation increased 2 [*PMS2*]) and indicate the possibility of an inherited cancer predisposition syndrome regardless of the family history of cancer. Patients should be counseled about this possibility **prior to** tumor/somatic sequencing and, if results are suggestive, referral to genetic counseling for dedicated/confirmatory germline genetic testing. (See 'Implications of somatic tumor genomic testing' above.)

- When considering the risk of developing prostate cancer, a genetic test that does not identify a cancer predisposition gene mutation does not negate the contribution to risk conferred by a strong family history of cancer. (See 'Impact of family history' above.)

- **Implications for prostate cancer screening**

  - There is variability in the prostate cancer screening and early detection guidelines for males at increased risk due to family history and/or known inherited pathogenic mutations from many professional societies. Data from the Identification of Men with a Genetic Predisposition to Prostate Cancer (IMPACT) study that the cancer detection rate is substantially elevated *in BRCA2, MSH2, and MSH6* pathogenic variant (mutation) carriers at a prostate-specific antigen (PSA) level >3 ng/mL have helped to establish the importance of close PSA screening in these males.

  - We advise consultation at a center of excellence and recommend participation in clinical trials testing screening strategies (when possible). If clinical trial participation is not feasible, our approach is outlined in the table (table 4). (See 'Screening implications of increased genetic risk' above.)

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GRAPHICS

Suggested criteria for referral to a genetics professional[1-4]

Male WITHOUT a diagnosis of prostate cancer and any 1 of the following:	Male WITH a diagnosis of prostate cancer and any 1 of the following:
▪ Known mutation in a cancer susceptibility gene within the family	▪ Known mutation in a cancer susceptibility gene within the family
▪ Family history suggestive of hereditary breast and ovarian cancer syndrome • ≥2 breast cancers in a single person (close relative) • ≥2 family members with breast cancer on the same side of the family, at least 1 diagnosed ≤50 years of age • Close relative with ovarian cancer • Close relative with male breast cancer • Family history of ≥3 of the following, especially if diagnosed ≤50 years and/or with multiple primary cancers: breast cancer, ovarian cancer, pancreas cancer, prostate cancer (Gleason ≥7 and/or WHO Grade Group ≥2), melanoma, colon cancer, etc	▪ Family history suggestive of hereditary breast and ovarian cancer syndrome • FDR or personal history of male breast cancer • Family history of ≥2 close relatives with either breast or prostate cancer (any grade) at any age • FDR and second-degree relatives with exocrine pancreas cancer and prostate cancer (metastatic, intraductal/cribriform, or NCCN guidelines for prostate cancer – high- or very high-risk group) • Consider for those with Ashkenazi Jewish ancestry • FDR diagnosed with ovarian cancer (including fallopian tube cancer or peritonea cancer), exocrine pancreatic cancer • Probability >5 % of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)
▪ Family history suggestive of Lynch syndrome • ≥1 FDR with colorectal or endometrial cancer diagnosed <50 years • ≥1 FDR with colorectal or endometrial cancer **and** another synchronous or metachronous Lynch-syndrome-related cancer, or ≥2 family members with any of the following: colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), small intestinal, sebaceous carcinomas and keratoacanthomas	▪ Family history suggestive of Lynch syndrome • ≥1 FDR (especially if diagnosed <50 years) with colorectal, endometrial, gastric, ovarian pancreas, urothelial, brain (usually glioblastoma), biliary tract, and small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome. With any of the following: colorectal, endometrial, gastric, ovarian, pancreases, ureter and renal pelvis, brain (usually glioblastoma), small intestinal,

	sebaceous carcinomas and keratoacanthomas
▪ Family history suggestive of hereditary prostate cancer syndrome • ≥2 prostate cancers on the same side of the family • FDR who died as a result of prostate cancer <60 years of age • FDR diagnosed with prostate cancer ≤55 years of age	▪ Family history suggestive of hereditary prostate cancer syndrome • ≥2 prostate cancers on the same side of the family • FDR who died as a result of PCa <60 years • FDR diagnosed with PCa ≤55 years • Personal history of PCa diagnosed ≤55 years **and** an FDR with PCa at any age
	▪ Personal history of tumor (somatic) sequencing indicating presence of mutations in hereditary cancer risk genes (eg, *BRCA2*, *BRCA1*, *ATM*, *MSH2*, *MSH6*, *MLH1*, *PMS2*)
	▪ Personal history of PCa or other cancer with MMR deficiency determined by PCR, NGS, or IHC
	▪ Personal history of metastatic PCa
	▪ Personal history of high-risk and very high-risk localized PCa, and/or intraductal or cribriform histology

WHO: World Health Organization; FDR: first-degree relative; *BRCA*: breast cancer susceptibility gene; PCa: prostate cancer; *ATM*: ataxia telangiectasia mutated; *MSH*: mutS homolog; *MLH1*: mutL homolog 1; *PMS2*: postmeiotic segregation increased 2; MMR: mismatch repair; PCR: reverse-transcriptase polymerase chain reaction; NGS: next generation sequencing; IHC: immunohistochemistry.

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Graphic 116321 Version 4.0

ISUP grade group classification system

Grade group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

ISUP: International Society of Urological Pathology.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

Graphic 107132 Version 2.0

Germline inherited genes with possible treatment ramifications in metastatic prostate cancer

Gene	Association with increased prostate cancer risk	Association with other cancer risk (eg, breast, ovary, colon, uterus) and management options	Prevalence of germline mutations in metastatic prostate cancer	Prevalence of germline mutations in prostate cancer with family history	Treatment implicatic metastatic prostate c	
					Eligible for DNA-damaging agents: PARP inhibitor, platinum	Eligible immunoth PD-1 inhi
ATM	X	X	1.6%	2.0%	**X**	
BARD1					**X**	
BRCA1	X	X	0.9%	0.7%	**XX**	
BRCA2	X	X	5.4%	4.7%	**XX**	
BRIP1					**X**	
CDK12					**X**	
CHEK1					**X**	
CHEK2	X	X	1.9%	2.9%	**X**	
FANCL					**X**	
HOXB13	X		Not evaluated	1.1%		
MLH1	X	X		0.1%		**X**
MSH2	X	X	0.1%	0.7%		**X**
MSH6	X	X	0.1%	0.5%		**X**
NBN		X	0.3%	0.3%	**X**	
PALB2		X	0.4%	0.6%	**X**	
PMS2	X	X	0.3%	0.5%		**X**
RAD51B					**X**	
RAD51C		X	0.1%	0.2%	**X**	
RAD51D		X	0.4%	0.2%	**X**	
RAD54L					**X**	

In the column entitled Eligible for DNA damaging agents: PARP inhibitor, platinum: **XX** denotes those pathogenic variants that have FDA approval for rucaparib and olaparib; **X** denotes FDA approval for olaparib.

PARP: poly-adenosine diphosphate-ribose polymerase; PD-1: programmed cell death 1; *ATM*: ataxia telangiectasia mutated; *BARD1*: BRCA1-associated RING domain 1; *BRCA*: breast cancer susceptibility gene; *BRIP*: BRCA1-interacting protein c-terminal helicase-1; *CDK*: cyclin-dependent kinase; *CHEK*: checkpoint kinase; *HOXB13*: homeobox B13; *MLH1*: mutL homolog 1; *MSH*: mutS homolog; *NBN*: nibrin; *PALB2*: partner and localizer of *BRCA2*; *PMS2*: postmeiotic segregation increased 2; *RAD*: recombination protein A; FDA: US Food and Drug Administration.

Graphic 126461 Version 5.0

Recommended approach to prostate cancer screening in high-risk men with ar inherited predisposition to prostate cancer

For males with a personal history of *BRCA1/2* mutation, Lynch syndrome, or pathogenic variants in other prostate cancer-associated risk genes:
Begin screening at 40 years of age (*BRCA2*); for other high-risk pathogenic variants, shared decision making on risks and benefits of screening beginning at age 40 to 45.*
For most, screening consists of annual PSA and DRE.
Influence of PSA level on frequency of screening: ▪ Males who have a PSA above the median for their age group are at higher risk for prostate cancer and aggressive prostate cancer; the higher above the median, the greater the risk. ▪ If the PSA is below the age-adjusted median and there is no other indication for biopsy, repeat screening in 12 months. ▪ If the PSA is above the age-adjusted median, recheck the PSA in 6 to 12 months; if increased, consider extended pattern biopsy with mpMRI or TRUS guidance. ▪ Any PSA >3 ng/mL or abnormal findings on DRE should prompt a biopsy. A lower cutpoint for biopsy may be considered in males at higher risk, after accounting for age-based normal ranges.
Upper limit of age-adjusted median PSA range: ▪ ≤49 years: PSA 1.5 ng/mL ▪ 50 to 59 years: PSA 2.0 ng/mL ▪ 60 to 69 years: PSA 2.5 ng/mL

BRCA: breast cancer susceptibility gene; PSA: prostate-specific antigen; DRE: digital rectal examination; mpMRI: multiparametric magnetic resonance imaging; TRUS: transrectal ultrasound; HOXB13: homeobox B13; MSH: mutS homolog; TP53: tumor protein p53.

* For most males with high-risk conditions, we recommend participation in a clinical trial of screening, where possible. Germline abnormalities in *BRCA2* have the most evidence for elevated risk and poorer prognosis, and all affected males are recommended to start screening at age 40. Other germline prostate cancer risk variants that could be considered for this approach include *HOXB13*, *MSH6*, *MSH2*, and *TP53*. The presence of a strong family history (even without a known germline pathogenic or likely pathogenic variant) should also prompt shared decision making around modified screening.

Graphic 126446 Version 4.0

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