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Authors
Carroll, Peter R
Parsons, J Kellogg
Andriole, Gerald
et al.

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NCCN Guidelines® Insights Prostate Cancer Early Detection, Version 2.2016:

Featured Updates to the NCCN Guidelines

Peter R. Carroll, MD, MPH[1,*], **J. Kellogg Parsons, MD, MHS**[2,*], **Gerald Andriole, MD**[3], **Robert R. Bahnson, MD**[4], **Erik P. Castle, MD**[5,*], **William J. Catalona, MD**[6,*], **Douglas M. Dahl, MD**[7], **John W. Davis, MD**[8,*], **Jonathan I. Epstein, MD**[9,*], **Ruth B. Etzioni, PhD**[10], **Thomas Farrington, BSEE**[11,*], **George P. Hemstreet III, MD, PhD**[12], **Mark H. Kawachi, MD**[13], **Simon Kim, MD, PhD**[14], **Paul H. Lange, MD**[15,*], **Kevin R. Loughlin, MD**[16], **William Lowrance, MD, MPH**[17,*], **Paul Maroni, MD**[18,*], **James Mohler, MD**[19,*], **Todd M. Morgan, MD**[20], **Kelvin A. Moses, MD, PhD**[21], **Robert B. Nadler, MD**[6,*], **Michael Poch, MD**[22], **Chuck Scales, MD**[23], **Terrence M. Shaneyfelt, MD, MPH**[24,*], **Marc C. Smaldone, MD, MSHP**[25,*], **Geoffrey Sonn, MD**[26,*], **Preston Sprenkle, MD**[27], **Andrew J. Vickers, PhD**[28], **Robert Wake, MD**[29,*], **Dorothy A. Shead, MS**[30,*], **Deborah A. Freedman-Cass, PhD**[30,*]

[1]UCSF Helen Diller Family Comprehensive Cancer Center

[2]UC San Diego Moores Cancer Center

[3]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

[4]The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

[5]Mayo Clinic Cancer Center

[6]Robert H. Lurie Comprehensive Cancer Center of Northwestern University

[7]Massachusetts General Hospital Cancer Center

[8]The University of Texas MD Anderson Cancer Center

[9]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

[10]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

[11]Prostate Health Education Network

[12]Fred & Pamela Buffett Cancer Center at The Nebraska Medical Center

[13]City of Hope Comprehensive Cancer Center

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[15]University of Washington Medical Center/Seattle Cancer Care Alliance

[16]Dana-Farber/Brigham and Women's Cancer Center

[17]Huntsman Cancer Institute at the University of Utah

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[22]Moffitt Cancer Center

[23]Duke Cancer Institute

[24]University of Alabama at Birmingham Comprehensive Cancer Center

[25]Fox Chase Cancer Center

[26]Stanford Cancer Center

[27]Yale Cancer Center/Smilow Cancer Hospital

[28]Memorial Sloan Kettering Cancer Center

[29]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

[30]National Comprehensive Cancer Network.

[*]Provided content development and/or authorship assistance.

Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection provide recommendations for prostate cancer screening in healthy men who have elected to participate in an early detection program. The NCCN Guidelines focus on minimizing unnecessary procedures and limiting the detection of indolent disease. These NCCN Guidelines Insights summarize the NCCN Prostate Cancer Early Detection Panel's most significant discussions for the 2016 guideline update, which included issues surrounding screening in high-risk populations (ie, African Americans, *BRCA1/2* mutation carriers), approaches to refine patient selection for initial and repeat biopsies, and approaches to improve biopsy specificity.

Overview

In men, prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death. Prostate cancer represents a spectrum of disease that ranges from nonaggressive and slow-growing disease that does not require treatment to aggressive and fast-growing disease that does necessitate treatment. Early detection strategies should maximize the detection of aggressive prostate cancer that is potentially curable, while

minimizing unnecessary procedures and the detection of indolent disease. Population-based prostate cancer screening studies have shown survival benefits using prostate-specific antigen (PSA) levels, sometimes in combination with a digital rectal examination or other ancillary tests.[1–5] Therefore, the NCCN Prostate Cancer Early Detection Panel supports the use of PSA testing for the early detection of prostate cancer in informed, healthy men in specific age groups and encourages active surveillance or observation for appropriate candidates in whom low-risk disease is identified (see the full NCCN Guideline recommendations online at NCCN.org).

The issues discussed by the panel this year are described in these NCCN Guidelines Insights. Changes to the NCCN Guidelines algorithms are indicated with blue font herein.

Patient Selection for Biopsies

PSA testing results in the diagnosis of high-grade tumors at a potentially earlier, more curable stage than clinical detection. However, PSA testing has poor specificity and often produces false-positive results, which contribute to patient anxiety and increased costs and potential complications associated with unnecessary biopsies (eg, drug-resistant *Escherichia coli* infections). PSA testing also leads to the detection of much indolent disease (overdetection), which contributes to overtreatment, patient stress, possible complications, and inconvenience of active surveillance. Additional techniques used with PSA testing have the potential to refine patient selection for biopsies, decrease unnecessary biopsies, reduce overdetection, and increase biopsy specificity, without missing a substantial number of aggressive cancers. Such improvements to PSA screening could make it a more valuable tool for men who choose to participate in an early detection program by increasing the benefits while decreasing the risks.

Therefore, the panel discussed the roles of biomarker testing and advanced imaging to refine patient selection for initial and repeat biopsies, as described herein.

Biomarker Tests

When a patient meets the standards for biopsy, patients and physicians may wish to further define the probability of cancer before proceeding to biopsy with its associated risks. Several biomarker tests have been developed with the goals of refining patient selection for biopsies, decreasing unnecessary biopsies, and increasing the specificity of cancer detection, without missing a substantial number of higher-grade (Gleason score ≥7) cancers. These tests may be especially useful in men with PSA levels between 3 and 10 ng/mL. Most often, these tests have been used in patients with one negative biopsy to determine whether repeat biopsy is an appropriate consideration.

In the 2015 version of these guidelines, the panel recommended consideration of percent free PSA, 4Kscore, or Prostate Health Index (PHI) in patients with PSA levels greater than 3 ng/mL who have not had a biopsy. For men who have had at least one prior negative biopsy and are thought to be at higher risk, the panel recommended the same tests or PCA3.[6–16]

Multiple institutional review comments requested that the panel consider adding ConfirmMDx in the repeat biopsy setting based on data showing that it has potential value for patients with an elevated PSA and prior negative biopsy. ConfirmMDx is a tissue-based, multiplex epigenetic assay that aims to improve the stratification of men being considered for repeat biopsy. Hypermethylation of the promoter regions of *GSTP1*, *APC*, and *RASSF1* are assessed in core biopsy tissue samples.[17,18] The panel found the available data convincing and unanimously agreed (with several abstentions) to add consideration of ConfirmMDx for men contemplating repeat biopsy (see PROSD-4; above).

The panel then discussed how to compare the various recommended tests and whether they could recommend one or more tests over the others. As the list of potential assays grows, the NCCN Guidelines Panel believes that clinicians and patients will need more guidance. These tests have different objectives (eg, improving sensitivity, reducing false-positives), different impacts on downstream outcomes (eg, mortality reduction, reduced overdiagnosis), and are used in different settings (ie, initial or repeat biopsy). Ideally, the negative predictive value and positive predictive value (PPV) for any cancer and for high-grade cancer; the number of biopsies avoided; and the number of aggressive cancers missed for each test could be compared. However, studies for the different assays have been performed with different cohorts, settings, time points, and reported outcomes. Head-to-head comparisons have been performed in Europe for some of these tests, used independently or in combinations in the initial or repeat biopsy settings, but sample sizes were small and results varied.[19–26]

Therefore, the panel emphasized the following points: no biomarker test can be recommended over any other; a biomarker assay can be performed in addition to multiparametric MRI (mp-MRI)/refined biopsy techniques in the repeat biopsy setting (discussed in the following section); the optimal order of biomarker tests and imaging is unknown; and it remains unclear how to interpret results of multiple tests in individual patients, especially when results are contradictory. The panel further emphasized that results of any of these tests, when performed, should be used as part of discussions between clinician and patient to assist in decisions regarding whether to proceed with biopsy.

Multiparametric MRI

Considerable interest exists for the use of novel MRI, most notably mp-MRI, to select patients who need a prostate biopsy or to guide needle placement during the procedure, although data supporting its use in these settings are currently limited.[27–29] The goals of using MRI to inform the decision of whether to perform a biopsy include reducing the number of men undergoing biopsy, reducing the detection of indolent disease (and thus the risks of overdetection and overtreatment), and improving the detection of clinically significant disease through targeted biopsies (see “Advanced Biopsy Techniques,” this page).

The panel discussed the use of MRI before initial biopsy based on the available data analyzing the clinical utility of mp-MRI for patient selection in the initial biopsy setting. In a prospective study of 223 biopsy-naïve men with an elevated PSA level, all men underwent standard transrectal ultrasound (TRUS) biopsies in addition to mp-MRI.[28] Not performing a biopsy in men with PI-RADS 1/2 lesions on MRI would have reduced the number of men

requiring biopsy by 36%, reduced the identification of low-risk prostate cancer by 87%, and increased the yield of intermediate/high-risk tumors by 18%, but would have missed 15 intermediate/high-risk tumors (6.7% of study population). A trial at a single hospital-based practice randomized 130 biopsy-naïve men with elevated PSA levels to either TRUS-guided random biopsy alone or to prebiopsy mp-MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion targeted biopsy.[29] In this study, 13 tumors with Gleason score 3 + 4 would have been missed in the 53 evaluable men in the mp-MRI group based on MRI results (24.5%). Additional clinical trials are underway to assess the value of MRI for diagnosis in the prebiopsy setting (ClinicalTrials. gov identifiers: NCT02131207, NCT02485379, and NCT02450266).

Based on these studies, the panel agreed that the use of MRI to exclude men from biopsies could lead to many clinically significant cancers being missed. Overall, the panel believes that MRI alone should not be used to determine whether to perform an initial biopsy, and emphasizes that a negative MRI is not a reason to forego biopsy in men with strong indications for a first-time biopsy. All men with indications for biopsy should receive the standard 12-core TRUS-guided biopsy regardless of MRI results, with possible additional targeted biopsies. The panel therefore added a footnote stating that MRI is not currently routinely recommended before initial biopsy to accentuate these points (see PROSD-3; page 512). Additionally, the panel acknowledged emerging data showing that mp-MRI followed by lesion targeting may increase the detection of higher-risk disease while lowering the detection of lower-risk disease (see “Advanced Biopsy Techniques,” below).[30]

Advanced Biopsy Techniques

Targeted, template, and saturation biopsy techniques are being studied in hope of improving detection of clinically significant prostate cancer while minimizing the detection of indolent disease.[31–35] Targeted biopsy techniques include cognitive or visual targeting (ultrasound-guided, based on an MRI image), MRI/TRUS fusion platforms (merging a stored MRI image with a real-time ultrasound image), and direct in-bore magnetic resonance–guided biopsy (performed by an interventional radiologist while the patient is in the scanner).[31–33] In saturation biopsies, cores are systematically collected every few millimeters across the entire prostate to improve detection over that of a standard 12-core biopsy. Saturation biopsies can be performed via transrectal or transperineal approaches. Another advanced technique is transperineal template biopsy, which does not saturate every single area but instead systematically samples anterior, mid, posterior, and basal zones for approximately 24 to 32 cores.[36]

For the 2016 guideline update, the NCCN Guidelines Panel discussed the role of targeted biopsies in the initial and repeat settings, as described in these Insights.

Targeted Biopsies in the Initial Biopsy Setting

The panel discussed the data on targeted biopsy techniques for biopsy-naïve patients. In a prospective study of 223 biopsy-naïve men with elevated PSA levels, all men had standard TRUS biopsies and mp-MRI.[28] Participants with suspicious or equivocal lesions (PI-RADS 3–5) then underwent MRI-guided biopsy. TRUS biopsies detected 126 of 142 cases (88.7%),

including 47 cases classified as low risk. The MRI-guided biopsies identified an additional 16 cases of intermediate/high-risk prostate cancer and led to the reclassification of 13 cases from low risk to intermediate/high risk. Therefore, the addition of mp-MRI with targeted biopsies for suspicious or equivocal lesions to standard biopsy allowed the identification of clinically significant disease in an additional 13% of the study population. A single-center trial randomized 130 biopsy-naïve men to receive either TRUS-guided random biopsy alone or prebiopsy mp-MRI, TRUS-guided random biopsy, and cognitive MRI/TRUS fusion targeted biopsy.[29] Similar rates of detection of prostate cancer (64% vs 57%; P=.5) and clinically significant cancer (55% vs 45%; P=.8) were seen in the 2 arms.

In a single-institution prospective cohort study, 1,003 men with elevated PSA levels or an abnormal digital rectal examination and lesions visible on mp-MRI underwent both MRI/ultrasound fusion targeted and standard biopsy.[30] In this study, 196 men had no prior biopsy, and results appear to be similar in the biopsy-naïve subgroup compared with the entire cohort. In the full cohort, 170 men had pathology results available after radical prostatectomy: 8 men (4.7%) had intermediate- or high-risk cancers that would have been missed based on targeted biopsy results of no or low-risk cancer, and 44 men (26%) had intermediate- or high-risk cancers that would have been missed based on standard biopsy results of no or low-risk cancer. The sensitivities of targeted and standard biopsies for detecting intermediate- or high-grade cancer were 77% and 53%, respectively, whereas the specificities of the approaches were similar, at 68% and 66%, respectively. Combining both biopsy techniques increased sensitivity to 85% but decreased specificity to 49%. The effect of targeted biopsies on clinical outcomes is still unknown.

The panel did not believe that the current data for the use of targeted biopsies in the initial biopsy setting were sufficient to recommend them over standard biopsies in this setting. However, the panel agreed that it was important to acknowledge the emerging data showing that mp-MRI followed by lesion targeting may increase the detection of clinically significant, higher-risk disease (Gleason ≥4 + 3) while lowering the detection of lower-risk disease (Gleason 6 or lower-volume 3 + 4) (see PROSD-3; page 512).

Targeted Biopsies in the Repeat Biopsy Setting

A negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy, and repeat biopsies are often considered in men for whom clinical suspicion of high-risk disease persists. Reviewers requested that the NCCN Guidelines Panel consider the addition of mp-MRI–guided biopsy techniques for patients with prior negative biopsies and for patients in whom a high suspicion exists for clinically significant prostate cancer. These individuals pointed out that increasing data are demonstrating the superiority of MRI-targeted biopsy techniques over standard biopsy for the detection of clinically significant/high-grade prostate cancer after a negative biopsy, and therefore requested that the panel consider putting more emphasis on these approaches by adding them to the algorithm. The panel was also asked to consider where targeted biopsy belonged in the diagnostic algorithm relative to the recommended biomarkers assays in this repeat biopsy setting.

In a prospective study that included 347 patients with findings suspicious for prostate cancer, many of whom had 1 or more previous negative biopsies, all patients received mp-MRI

and those with abnormal findings proceeded to MRI/TRUS fusion targeted biopsies.[27] The outcome was defined as improved detection in targeted cores, with significantly more cancer detected in targeted cores than in systematic biopsies (30% vs 8.2%). Approximately 12% of men without MRI-suspicious lesions were diagnosed with intermediate-risk tumors. In this study, the cancer detection rate was 51% in men with previous negative biopsies. In a prospective cohort study of 1,003 men undergoing both MRI-targeted and standard biopsy (see "Targeted Biopsies in the Initial Biopsy Setting," page 515), Siddiqui et al[30] noted that targeted biopsies were associated with the detection of high-risk cancer and decreased detection of low-risk cancer.[30] A recent meta-analysis of 16 studies (1,926 men) also showed that MRI-targeted biopsy improved detection of clinically significant prostate cancer in biopsy-naïve men compared with standard TRUS biopsy.[37]

Although the NCCN Guidelines Panel found the increasing evidence convincing, they also pointed out that the publications come from only a few centers with a small number of clinicians and radiologists. No data to date show that these techniques will work in other oncology settings (eg, community hospitals). Overall, the panel believes that the level of evidence has risen to the level needed for targeted biopsies to be considered in the repeat biopsy setting. The panel agreed to add mp-MRI and/or refined biopsy techniques for consideration in men with benign findings or focal high-grade prostatic intraepithelial neoplasia (see PROSD-4; page 513). These techniques include saturation biopsy strategies and the use of mp-MRI followed by a targeted biopsy technique based on the results, and these techniques can be considered before or after biomarker tests (discussed previously) to aid in patient/clinician discussions.

Screening in High-Risk Populations

Certain populations (eg, African Americans, men with a first-degree relative with prostate cancer) have a higher risk of developing prostate cancer.[38–42] At the meeting for the 2016 guideline update, the panel discussed the role that race and genetic susceptibility play in prostate cancer and whether or not screening recommendations should be altered for high-risk men.

Race

African American men have a 64% higher incidence of prostate cancer and 2.3-fold increase in prostate cancer mortality compared with white men, and are approximately 4 times more likely to be diagnosed with metastatic disease.[38,43] Furthermore, autopsy data indicate that prostate cancer may undergo transformation to aggressive disease earlier in African American men than in white men.[43] Factors that contribute to this racial disparity may include differences in genetic risk factors, environmental exposures, and patient and physician behaviors; decreased access to high-quality health care, including cancer early detection and follow-up care; delays in diagnosis; and suboptimal treatment.[44–47]

Two institutional reviewers introduced the topic of prostate cancer early detection in African Americans. In particular, they questioned whether discussions about screening should be initiated earlier with this population, if screening should start earlier in this group, and whether these men should be screened more intensively. The panel discussion that ensued

found a lack of data to inform the best strategy for prostate cancer screening in these men. Prostate cancer screening has been best studied in white men; data on screening in diverse and high-risk populations are lacking. In the PLCO trial, approximately 4.4% of the participants were African American and 6.9% had a positive family history, but no subset analyses were performed for black men.[48] In the ERSPC trial, no information on race or family history was reported.[3]

The panel discussed data suggesting that African American men have an earlier onset of prostate cancer, which might support earlier screening initiation. An analysis of SEER data from 2010 found that non-Hispanic black men were diagnosed with prostate cancer an adjusted average of 1.2 years earlier than non-Hispanic white men,[49] whereas an older SEER analysis found that African American men were diagnosed at an average of 3 years younger than white men.[50] A retrospective population-based cohort study in the United Kingdom found that black men were diagnosed an adjusted average of 5.1 years earlier than white men.[51] Another study estimated that African American men have an almost 2-fold higher risk of being diagnosed with prostate cancer before the age of 45 years compared with white men.[50]

Although the panel members agreed that this topic cannot and should not be ignored, they believe that data do not support earlier or more intensive screening at this time. Race is, however, included as a baseline evaluation factor for risk assessment that can be used to help decide when a man should begin the early detection process within the NCCN recommended ages of 45 to 75 years. Clearly, African American men are at a higher risk for prostate cancer and prostate cancer mortality, but the effects of earlier or more intensive screening on cancer outcomes and screening-related harms in this populations are not clear. The panel also noted that a baseline PSA value is a stronger predictive factor than a positive family history or race.[52] Therefore, although these individuals may require a higher level of vigilance and potentially different considerations when analyzing the results of screening tests, the panel did not provide separate screening recommendations for this patient population at this time. Instead, they added a footnote to emphasize these points (see PROSD-2; page 511).

BRCA1 and *BRCA2* Mutations

Germline *BRCA1* and *BRCA2* mutations (associated with hereditary breast and/or ovarian cancer syndrome) have been associated with an increased risk for prostate.[53–61] In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association between *BRCA1* mutations and an increased risk for prostate cancer is less consistent.[54,56,57,61–63] Furthermore, prostate cancer in men with germline *BRCA* mutations appears to have a more aggressive phenotype and is associated with significantly reduced survival times than prostate cancer in those who do not have the gene.[64–68]

The panel received an external submission requesting that genetic risk assessment be recommended in the NCCN Guidelines for Prostate Cancer Early Detection based on recommendations in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. These latter guidelines include personalized risk assessment, genetic

counseling, and possible genetic testing for individuals with a personal history of prostate cancer and 1 or more close blood relatives with breast cancer (age ≤50 years) or ovarian cancer, or 2 relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7). Individuals meeting these criteria are considered at risk of harboring a *BRCA1/2* mutation.[69] These guidelines note that individuals with a family history only can also be considered for genetic testing if no living affected family member is available, but that the limitations of testing in unaffected relatives should be discussed.[69]

Although the panel did not believe that the NCCN Guidelines for Prostate Cancer Early Detection should list recommendations for genetic risk assessment, they did agree that men should be asked about the presence of known *BRCA1/2* mutations in their families. Therefore, the panel added "Family history of *BRCA1/2* mutations" to the baseline evaluation that precedes discussions on the risks and benefits of prostate cancer screening (see PROSD-2; page 511). If there is a known or suspected cancer susceptibility gene, referral to a cancer genetics professional is recommended. Information regarding *BRCA1/2* gene status should be used as part of the discussion about prostate cancer screening; patients may not be aware of the increased risk of prostate cancer associated with these mutations. Some panel members believe that men with known germline *BRCA1/2* mutations should be encouraged to undergo PSA testing.

The panel then discussed whether a known *BRCA1* or *BRCA2* mutation would impact prostate cancer screening. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at NCCN.org) recommend that men with *BRCA2* mutations begin prostate cancer screening at age 40 years and that those with *BRCA1* mutations consider the same.[69] Results were recently reported from the first round of screening in the IMPACT study, which enrolled men aged 40 to 69 years with germline *BRCA1/2* mutations and a control group of men with wild-type *BRCA1/2* related to mutation carriers.[70] Although no difference was shown between carriers and controls in the rate of prostate cancer detection or the PPV of biopsy for detecting cancer in men with PSA levels greater than 3.0 ng/mL, a significant difference was seen in the PPV of biopsy for detecting intermediate/high-grade cancer in *BRCA2* carriers with PSA levels greater than 3.0 ng/mL (2.4% vs 0.7%; P=.04). Future rounds of screening in this trial may help inform the best strategy for screening in this high-risk population. Therefore, the panel noted that, although these mutations are clearly risk factors, data supporting a change in the PSA screening and biopsy recommendations for these men relative to those without mutations are insufficient at this time. The panel also noted that, as with race, baseline PSA value is a stronger predictive factor than a positive family history.[52]

Conclusions

The NCCN Guideline revisions for the 2016 update highlight several techniques designed to improve the identification of significant cancer while avoiding the detection of indolent disease. Advanced biopsy techniques, including targeted biopsies, are one promising technique to help advance these goals. In addition, patient selection for biopsies can be refined through the appropriate use of biomarker assays and advanced imaging, thereby minimizing unnecessary procedures and limiting the detection of indolent disease. In the

future, data may inform more individualized, risk-based approaches to prostate cancer early detection that take into account race, genetic predisposition, and family history.

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Editor:

Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE Authors:

Deborah J. Moonan, RN, BSN, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:

Peter R. Carroll, MD, MPH, Panel Chair, has disclosed that he receives consulting fees and/or honoraria from Genomic Health, Inc. and Janssen Pharmaceutica Products, LP; and grant/research support from Genomic Health, Inc. and Myriad Genetic Laboratories, Inc.

J. Kellogg Parsons, MD, MHS, Panel Vice Chair, has disclosed that he receives consulting fees and/or honoraria from MDx Health.

Erik P. Castle, MD, Panel Member, has disclosed that he has no relevant financial relationships.

William J. Catalona, MD, Panel Member, has disclosed that he received grant/research support from and served as a scientific advisor for Beckman-Coulter Inc.

John W. Davis, MD, Panel Member, has disclosed that he receives consulting fees and/or honoraria from Intuitive Surgical, Inc. and Myriad Genetic Laboratories, Inc.

Jonathan I. Epstein, MD, Panel Member, has disclosed that he is a consultant for Metamark Genetics, Inc. and Dianon Pathology.

Thomas Farrington, BSEE, Panel Member, has disclosed that he has no relevant financial relationships.

Paul H. Lange, MD, Panel Member, has disclosed that he has no relevant financial relationships.

William Lowrance, MD, MPH, Panel Member, has disclosed that he receives grant/research support from Myriad Genetic Laboratories, Inc. and Argos Therapeutics, Inc.; and is on the advisory board for Myriad Genetic Laboratories, Inc. and MDx Health.

Paul Maroni, MD, Panel Member, has disclosed that he has no relevant financial relationships.

James Mohler, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Robert B. Nadler, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Terrence M. Shaneyfelt, MD, MPH, Panel Member, has disclosed that he has no relevant financial relationships.

Marc C. Smaldone, MD, MSHP, Panel Member, has disclosed that he has no relevant financial relationships.

Geoffrey Sonn, MD, Panel Member has disclosed that he has no relevant financial relationships.

Robert Wake, MD, Panel Member has disclosed that he has no relevant financial relationships.

Dorothy A. Shead, MS, Director, Patient & Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

Deborah A. Freedman-Cass, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.