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Genomic Biomarkers for Clinically Localized Prostate Cancer*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe all the National Comprehensive Cancer Network approved genomic biomarkers available for clinically localized prostate cancer, their scientific rationale, describe the relevant evidence supporting their use, identify their limitations and apply them in the appropriate clinical scenario.

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INTRODUCTION

Since the prostate specific antigen era, there has been an increased incidence of indolent low risk, clinically localized prostate cancer.[1, 2] In response, landmark studies established treatment approaches based on broad risk grouping.[3] Despite these efforts, current risk stratification is still limited to definitively assess a patient's prognosis.[4] This is likely due to significant intra-group tumor biological and clinical heterogeneity resulting in disparate key oncologic outcomes.[5–9] Thus, the dilemma currently in clinically localized prostate cancer is balancing the importance of timely diagnosis and effective treatment of potentially lethal cancers with equal concerns of unnecessary biopsies, treatment and treatment related side effects.[10]

There are a number of approaches to risk stratification that rely on clinical and pathological factors alone. The National Comprehensive Cancer Network (NCCN) and the American Urological Association (AUA) stratify clinically localized prostate cancer into risk categories based on PSA, Gleason grade, amount of cancer, clinical examination and staging data to inform prognosis.[11] NCCN very low, low, favorable intermediate, unfavorable intermediate, high risk and very high risk disease are well validated and can help guide appropriate management strategies. Risk calculators such as CAPRA (University of California Cancer of the Prostate Risk Assessment) score and multivariable models such as the Memorial Sloan Kettering Cancer Center nomogram have similar intent, but these provide more granular risk stratification.[12, 13] Despite numerous models, current risk stratification remains limited, and clinical scenarios arise where additional information may be valuable. **Two common scenarios include: 1) choosing between active surveillance and primary treatment (radical prostatectomy or radiotherapy) for patients with high volume, low risk or favorable intermediate risk disease, and 2) determining which patients may benefit from adjuvant vs salvage radiation following prostatectomy.**

Another approach to risk stratification is to incorporate molecular data, either in isolation or as part of multivariable models that also include clinical information. RNA-based gene expression data from tissue have been a particular focus, as methods for extracting nucleic acids from formalin-fixed, paraffin-embedded tissue have become increasingly reliable over the past 1 to 2 decades. This has led to the development of clinical assays, not just in prostate cancer, but also in localized breast and colon cancer, informing a range of clinical decisions. In breast cancer, several gene expression panels, such as Oncotype DX®, MammaPrint®, PAM50, EndoPredict®, Breast Cancer Index™ and Genomic Grade Index, have demonstrated clinical utility in predicting disease recurrence and cost-effectiveness compared to uniform adjuvant therapy.[14, 15] The landmark TAILORx randomized trial demonstrated use of Oncotype DX to assess the risk of cancer recurrence can spare women unnecessary treatment.[16] Similar panels are used in colon cancer, such as ColoPrint® and Oncotype DX.[17, 18] In this Update we focus on the commercially available tissue based biomarkers for clinically localized prostate cancer.

CONFIRMMDX®

ConfirmMDx is an assay used on noncancerous biopsy tissue that identifies hypermethylation patterns of specific CpG islands (areas of higher cytosine and guanine base pairs) within GSTP1, APC and RASSF. Interestingly, hypermethylation of these genes is associated with a higher risk of *nearby* prostate cancer due to the "field effect" in which there are molecular changes in histologically normal tissue adjacent to cancerous cells. For each biopsy sample, ConfirmMDX is reported as either positive (suggestive of unbiopsied malignancy nearby) or DNA methylation negative (benign/normal state). If positive, the report includes the location of the abnormal biopsy and the likelihood of any prostate cancer or clinically significant prostate cancer if a patient is to undergo repeat biopsy. **ConfirmMDx is indicated for men with a negative biopsy within the previous 30 months and ongoing clinical suspicion of prostate cancer who are considering repeat biopsy or magnetic resonance imaging compared to routine screening.** According to manufacturer (MDxHealth®) figures, the cost of the assay is $2,472 for a panel of 12 cores and is covered by Medicare.

ConfirmMDx was validated in several studies demonstrating a negative predictive value between 88% and 90% for any prostate cancer compared to negative predictive value of 70% with biopsy alone.[19, 20] The test was found to have a higher negative predictive value (96%) when considering only clinically significant prostate cancer (defined as Gleason ≥7), compared to the 82% negative predictive value from biopsy alone.[21] This led to a hazard ratio (HR) of 3.3 and 5.0 for reduction of unnecessary biopsies when compared to using clinical and pathological variable and PSA alone, respectively. Overall, ConfirmMDx can be helpful for some men to avoid a repeat biopsy, but there are no data indicating a significant change in rates of metastasis or disease specific mortality (Appendix 1).

DECIPHER®

DECIPHER is a tissue based platform (biopsy or radical prostatectomy) that measures the microarray based expression of 22 genes regulating cell proliferation, differentiation, immune modulation and androgen receptor signaling. **The DECIPHER score is independent of clinical and demographic data, solely based on higher RNA levels found in more aggressive cancers and scored 0 to 1.0 with 3 risk categories: low (<0.45), intermediate (0.45–0.6) and high risk (>0.6).** The test is branded in 2 varieties, prostate biopsy and prostate RP, based on the tissue sample provided. However, the assays are identical, differing only slightly in reported measures**. DECIPHER prostate biopsy reports 1) percentage likelihood of high grade cancer (Grade Group 3 or higher), 2) 5-year metastatic risk and 3) 10-year disease-specific mortality.** DECIPHER prostate RP

ABBREVIATIONS: ASCO (American Society of Clinical Oncology), BCR (biochemical recurrence), CCP (cell cycle progression), GG (grade group), GPS (genomic prostate score), MRI (magnetic resonance imaging), NCCN (National Comprehensive Cancer Network), PSA (prostate specific antigen), RP (radical prostatectomy)

has been validated in patients with high risk of recurrence (T3a or higher, positive margins, high Gleason group or PSA persistent) and estimates metastatic and 10-year disease-specific mortality. DECIPHER is covered by Medicare for men with NCCN very low, low and intermediate risk prostate cancer, deciding between active surveillance and treatment or following prostatectomy for adverse pathology with an undetectable PSA to determine adjuvant vs salvage radiation therapy. The estimated cost is $5,100.

DECIPHER biopsy was initially validated in a small cohort of patients and outperformed NCCN risk grouping, PSA or biopsy Gleason score alone.[22] This has been validated to predict adverse pathology in low/favorable intermediate risk patients and metastatic disease in intermediate/high risk populations.[23] A meta-analysis of DECIPHER prostate RP studies showed the 5-year risk of metastatic disease following radical prostatectomy was 2.4%, 5.8% and 15.2% in DECIPHER low, intermediate and high risk patients, respectively.[24] In the same study, DECIPHER was found to be an independent predictor of metastasis in the setting of post-RP PSA persistence. Lastly, DECIPHER following prostatectomy demonstrated strong clinical utility in changing management recommendations for patients considering adjuvant vs salvage radiation therapy with decreased decisional conflict and anxiety.[25]

ONCOTYPE DX

Oncotype DX genomic prostate score is an RNA expression assay of 12 genes involved in androgen signaling, cellular organization, stromal response and cellular proliferation.[26] **The test is performed on biopsy samples and the GPS is scored 0 to 100 with higher numbers indicating "less favorable disease."** The number is then integrated with clinical information and the patient's cancer risk is categorized in a manner analogous to NCCN risk groups: very low, low, intermediate (subgrouped as favorable or unfavorable) and high. **The report also includes 1) risk of prostate cancer death within 10 years, 2) risk of metastasis within 10 years and 3) risk of adverse pathology (defined as Grade Group 3 or higher and/or pT3 disease or higher).** Indications for Oncotype DX are in the post-biopsy setting for a patient with low or favorable intermediate risk disease, deciding between active surveillance and treatment. While private insurance coverage varies, the estimated cost is $4,500 and covered by Medicare for patients with NCCN very low, low and favorable intermediate risk disease.

A number of publications have validated GPS as an independent predictor of adverse pathology, BCR, metastasis and cancer specific death.[27,28] A recent prospective validation study demonstrated GPS was an independent predictor of adverse pathology at prostatectomy for men with very low, low or favorable intermediate risk disease, reduced decisional conflict, and was reported as useful by 90% of patients and physicians.[29] GPS has also been validated in a diverse community care setting with 20% Black men, demonstrating similar value compared to White men.[30] A recent study suggests no utility in serial GPS (eg active surveillance) as changes in Gleason score or tumor volume cannot be reliably detected.[31]

PROLARIS®

Prolaris is an RNA expression assay of 31 cell cycle progression (CCP) genes, which are added together to calculate a CCP score.[32] **The test can be performed on biopsy tissue or radical prostatectomy, and the CCP score (modified since originally introduced) ranges from 0 to 10, with higher scores signifying more aggressive tumors. This score is combined with clinical and pathological variables to report 1) 10-year risk of disease specific mortality on active surveillance and 2) 10-year risk of metastasis after definitive treatment.** The primary use of this test is in the post-biopsy setting for a patient with low or favorable intermediate risk disease, aiding in the decision of active surveillance vs primary treatment. The assay has also been studied in the post-prostatectomy setting as a tool to inform use of adjuvant or salvage radiation therapy. Estimated cost is $3,900 and is covered by Medicare for patients with NCCN low and favorable intermediate risk disease with variable private insurance coverage.

A large body of retrospective data has shown the CCP score to be an independent predictor of BCR in patients undergoing radical prostatectomy.[33,34] CCP has been validated as an independent predictor of BCR following primary treatment and predicts risk of metastasis in patients with BCR.[35–37] One distinction of CCP score is validation in a cohort receiving radiation as primary therapy, independently predicting BCR.[38] CCP has also been studied from a clinical utility standpoint, and although the studies have substantial limitations, they suggest an increase in active surveillance among patients undergoing Prolaris testing.[39,40] In a cohort of men with newly diagnosed clinically localized prostate cancer, CCP has been associated with management decision changes in up to 65% of patients, with de-escalation of treatment representing the vast majority of those changes.[41,42]

PROMARK®

Unlike the previously described biomarkers, ProMark is a proteomic test measuring 8 protein biomarkers (DERL1, HSPA9, CUL2, FUS, SMAD4, PDSS2, pS6 and YBX1) that correlate with tumor aggressiveness. **The assay is obtained from biopsy tissue and scored from 0 to 100 with higher scores indicating higher likelihood of Grade Group 3 or higher and/or T3a or higher. The report includes the personalized risk of aggressive disease and the relative risk of aggressive disease compared to using only pathology data.[43]** This test can be considered in patients with low risk or favorable intermediate risk prostate cancer deciding between active surveillance and primary treatment. The estimated cost is $3,900 and is covered by Medicare, although private insurance coverage varies.

Relative to other biomarkers, ProMark has significantly fewer published data and is not widely utilized. The primary end point reported by the ProMark test is the risk of adverse pathology. The assay was clinically validated in 650 patients and better predicted risk of adverse pathology compared to NCCN and D'Amico risk categories.[44]

DISCUSSION

Within the emerging body of evidence suggesting clinical utility of these novel biomarkers, it is important to highlight some limitations. **Importantly there is no level I evidence to support use of these biomarkers.** While prospective studies have demonstrated the ability to reduce biopsies (ConfirmMDx), change decision making and reduce anxiety/decisional conflict (Prolaris, DECIPHER), there are no randomized controlled trials or

even observational data demonstrating use of the test improves quality of life or prostate cancer specific outcomes. While testing likely affects decision making, it is unknown yet whether those decisions are ultimately better (or worse) in terms of long-term oncologic outcomes when compared to decision making using existing pathological and clinical data. Additionally, there are limited data comparing the relative performance between these biomarkers, and therefore there can be no "gold standard." An additional concern regarding the performance of these tests is the existence of multifocality and intratumoral heterogeneity. If the biological index lesion is not biopsied and/or tested, then results of any of these tests may not represent the true disease state. Recent studies suggest specific cancer foci can have widely disparate risk profiles depending on which biomarker is used.[45] Some of the proprietary companies state the genomic results provide information on unsampled regions although a recent small study suggests otherwise (Appendix 2).[46]

There are ongoing efforts being made to test the clinical impact of these tests in men with localized prostate cancer. A randomized controlled trial titled Genomics in Michigan Impacting Observation or Radiation (G-MINOR) has completed enrollment and will report on the clinical utility of the DECIPHER test in high risk patients following prostatectomy in 2021.[47] Another prospective clinical trial (G-MAJOR: Genomics in Michigan to Adjust Outcomes in Prostate Cancer) is set to open this year and will test Oncotype Dx, DECIPHER and Prolaris in men with newly diagnosed low and intermediate risk prostate cancer. **It is also important to note the lack of robust evidence for use of biomarkers in non-White men, and there is some evidence suggesting differences in tumor biology between Black and White men.[48]** Data regarding the performance of molecular tests in Black populations at this point are underdeveloped.[49, 50] A recent study showed Oncotype Dx paradoxically reported worse prognosis for White men compared to Black men, while prognosis was similar for Prolaris and DECIPHER.[51]

These biomarkers were trained and validated in an era without routine MRI to guide biopsies, prior to the 2014 International Society of Urological Pathology modifications to Gleason grading and before molecular imaging for recurrent disease was widely available (eg fluciclovine, prostate specific membrane antigen). Image guided biopsies, particularly with repetitive sampling of specific areas, as well as a more restrictive definition of Gleason 6 (GG 1) and better understanding of variant patterns of Gleason pattern 4 (eg cribriform, intraductal) may alter the operating characteristics of a genomic biomarker.

Lastly, there are no data to suggest biomarkers are cost-effective or necessary for all patients diagnosed with localized prostate cancer or deciding between post-prostatectomy adjuvant vs salvage radiation. It is our impression the majority of clinical decisions can safely and effectively be made without the use of genomic biomarkers and the key question requiring further work is understanding which patients would benefit most from testing. The most common result of a genomic biomarker is no change in clinical risk profile, and we feel they should only be considered if the testing result will change clinical management, concordant with a recent American Society of Clinical Oncology (ASCO) guideline.[52] For example, the long-term safety and effectiveness of active surveillance for patients with very low or low risk prostate cancer using current risk stratification are well established, and we see a limited role for genomic biomarkers.[53–56] It is hard to envision a genomic biomarker improving the long-term cancer specific outcomes in low risk patients, but it may lead to more men undergoing earlier treatment. Thus, for patients with conventional very low or low risk prostate cancer, we feel active surveillance can be recommended with confidence without the need for further testing. While there are 2 cost modeling studies suggesting biomarkers could reduce costs, these can often exaggerate the cost savings because they assume overtreatment in majority of cases and overestimate the effectiveness of these tests in identifying high risk disease (Appendix 3).[57, 58]

We do envision a potential role for the emerging and important risk stratification of men with intermediate risk disease, specifically whether surveillance is a safe option (low genomic risk) and if treatment intensification is warranted (eg adding androgen deprivation therapy to radiation). It is our opinion the patients most likely to derive value from these biomarkers are patients with high volume, low risk or favorable intermediate risk disease who are choosing between active surveillance and primary treatment. Additionally these may also be appropriate for some patients with low risk disease who are risk averse and seeking further reassurance with their decision. Since all of the available biomarkers provide prognostic information and not specific predictive information on which treatment may be preferential, they may inform decisions on treatment intensification or relaxation, such as the role of androgen deprivation therapy or dose intensification with primary radiation.[59] There are data that DECIPHER may aid with the decision to pursue adjuvant vs salvage therapy following prostatectomy, although this may ultimately change since a recent trial suggested equivalent outcomes between adjuvant and early salvage radiation therapy (see figure).[60]

DID YOU KNOW

- NCCN and ASCO guidelines recommend considering use of genomic biomarkers during initial risk stratification for men with low or favorable intermediate risk prostate cancer considering active surveillance, when it is likely to affect management.
- NCCN and ASCO guidelines recommend considering use of the genomic biomarker DECIPHER following radical prostatectomy in patients with adverse pathology to help identify which patients may benefit from adjuvant/salvage therapy.
- There is currently no level I evidence supporting use of genomic biomarkers in clinically localized prostate cancer.

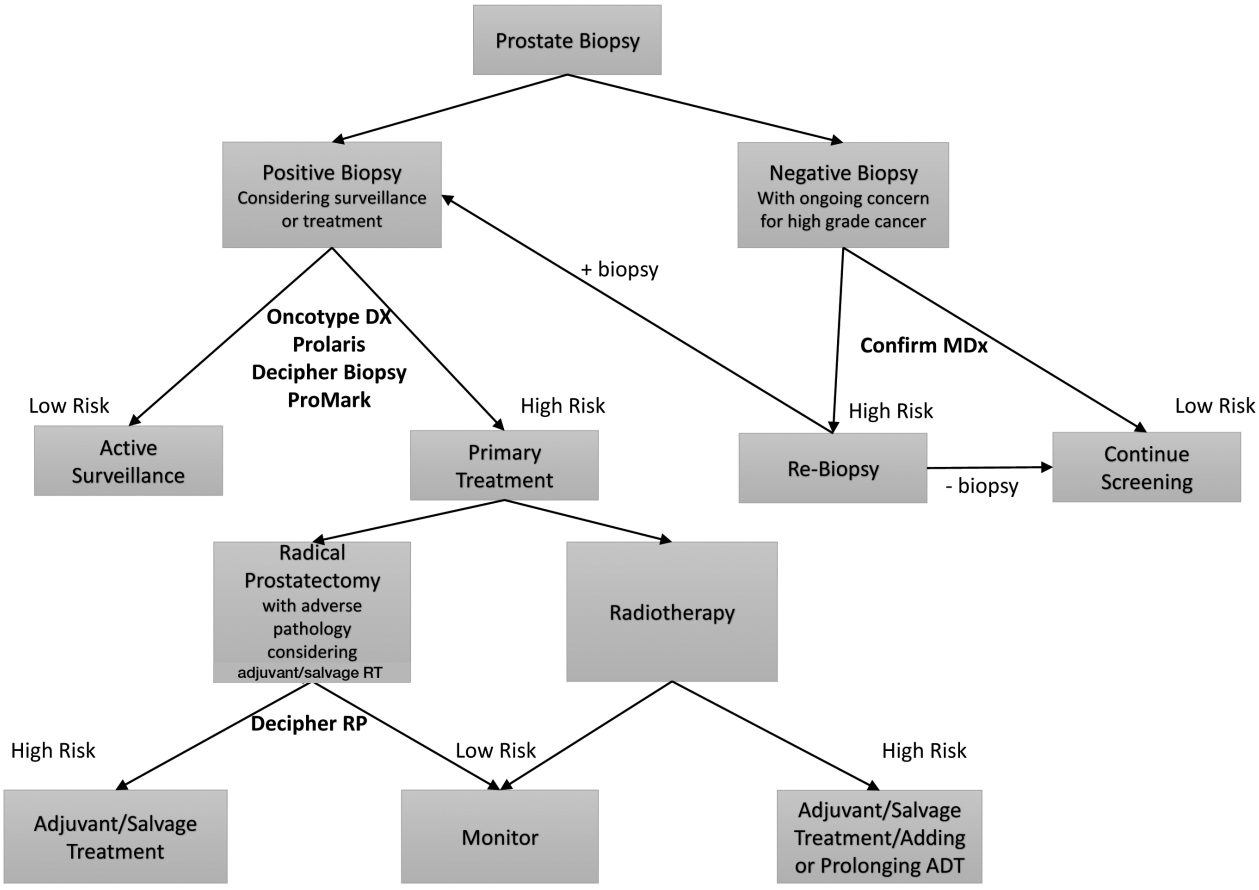

Figure. Flowchart of genomic biomarkers for clinically localized prostate cancer. Clinical scenarios in which they may be considered, as depicted in flowchart, are based on current National Comprehensive Cancer Network guidelines. RT, radiation therapy. ADT, androgen deprivation therapy.

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Appendix 1. Summary of tissue based genomic assays for clinically localized prostate cancer

Test	Mechanism	List Price	Indicated Patient Population	Indicated Clinical Scenario	Report	NCCN Recommendation
ConfirmMDx	Measures DNA hypermethylation pattern of CpG island promoter regions of GSTP1, APC and RASSF	$206 per core	Post negative prostate biopsy, wih suspicion of occult cancer	Re-biopsy/MRI vs monitor patient with negative biopsy despite high clinical suspicion of cancer	1. DNA methylation (positive or negative) 2. Likelihood of low risk vs clinically significant prostate cancer on repeat biopsy	Can be considered in patients thought to be higher risk despite negative prostate biopsy (2A)
DECIPHER	Measures RNA expression from 22 genes	$5,200	1. Low and favorable intermediate risk prostate cancer 2. Prostatectomy/ radiation patients at high risk for recurrence	1. Active surveillance vs primary treatment 2. Adjuvant/ salvage therapy vs monitoring	1. Score 0.0–1.0 2. Risk of high grade cancer at time of prostatectomy (primary Gleason 4 or 5) 3. 5-Year risk of metastasis after RP 4. 10-Year risk of disease specific mortality after RP	1. May be considered during initial risk stratification for men with low or favorable intermediate risk disease (2A) 2. May be considered during work up for post RP PSA persistence or recurrence (2B)
Oncotype DX GPS	Measures RNA expression from 17 genes over 4 pathways	$4,500	Low and favorable intermediate risk prostate cancer	Active surveillance vs primary treatment	1. Score 0–100 2. 10-Year risk of disease specific mortality 3. 10-Year risk of metastasis 4. Risk of adverse pathology (defined as primary Gleason 4 or higher and/or pT3 disease or higher)	May be considered during initial risk stratification for men with low or favorable intermediate risk disease (2A)
Prolaris CCP	Measures RNA expression from 31 cell cycle progression genes	$3,900	1. Low and favorable intermediate risk prostate cancer 2. Prostatectomy/ radiation patients at high risk for recurrence	1. Active surveillance vs primary treatment 2. Adjuvant/ salvage therapy vs monitoring	1. Score 0–10 2. 10-Year risk for disease specific mortality on active surveillance 3. 10-Year risk of metastasis after definitive treatment	May be considered during initial risk stratification for men with low or favorable intermediate risk disease (2A)

Appendix, *continued*

***Appendix**, continued*

ProMark	Measures expression of 8 proteins that correlate with tumor aggressiveness	$3,900	Patients with low and favorable intermediate risk prostate cancer	Active surveillance vs primary treatment	1. Score 0–100 2. Risk of aggressive disease (defined as Gleason 7 or higher and/or T3a or higher) 3. Relative risk of aggressive disease compared to using only pathologic data	May be considered during initial risk stratification for men with low or favorable intermediate risk disease (2A)

Appendix 2. NCCN prostate cancer guidelines regarding genomic biomarkers[10]

NCCN Guidelines Statement
1. Men with low or favorable intermediate-risk disease may consider the use of the following tumor-based molecular assays: DECIPHER, Oncotype DX Prostate, Prolaris and ProMark. Retrospective studies have shown that molecular assays performed on prostate biopsy or radical prostatectomy specimens provide prognostic information independent of NCCN or CAPRA risk groups. These include but are not limited to likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage. 2. The DECIPHER molecular assay can be considered for prognostication after radical prostatectomy.

Appendix 3. ASCO guidelines on molecular biomarkers in localized prostate cancer[52]

ASCO Guideline Statement on Molecular Biomarkers in Localized Prostate Cancer
1. In identifying patients who are most likely to benefit from active surveillance, or to diagnose clinically significant prostate cancer, commercially available molecular biomarkers (ie Oncotype DX Prostate, Prolaris, DECIPHER and ProMark) may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. Routine ordering of molecular biomarkers is not recommended. (Moderate Recommendation)
2. In guiding the decision of post-prostatectomy adjuvant versus salvage radiation, the panel recommends consideration of a commercially available molecular biomarker (eg DECIPHER Genomic Classifier) in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. In the absence of prospective clinical trial data, routine use of genomic biomarkers in the post-prostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered. (Moderate Recommendation)
3. In men with newly diagnosed prostate cancer eligible for active surveillance, both magnetic resonance imaging and genomics intend to identify clinically significant cancers. The Expert Panel endorses their use only in situations in which the result, when considered with routine clinical factors, is likely to affect management. This may include, for instance, the initial management of men who are potentially eligible for active surveillance, where each of these approaches may provide clinically relevant and actionable information. These tests may provide information independent of routine clinical parameters and independent of one another. (Weak Recommendation)

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1. The only biomarker indicated for patients with a negative prostate biopsy is
   a. ProMark
   b. Prolaris
   c. Oncotype DX
   d. ConfirmMDx

2. The only biomarker that is recommended by the NCCN and ASCO to risk stratify patients with adverse pathology following radical prostatectomy is
   a. Oncotype DX
   b. DECIPHER
   c. Prolaris
   d. ProMark

3. A 65-year-old man with a PSA 4.2 ng/dl is diagnosed with one core of GG 1 prostate cancer, with 10% core involvement on a transrectal ultrasound guided biopsy. He is interested in active surveillance, however asks if there is any test that may help determine if his cancer has a chance of being more aggressive. The next step is to advise him that
   a. active surveillance for very low risk prostate cancer is safe and effective with extensive level I evidence supporting its use. Further testing is unlikely to change management decisions
   b. Oncotype DX will quantify his 10-year prostate cancer mortality risk, thus determining if he needs treatment
   c. Prolaris as it has been validated to increase utilization of active surveillance
   d. MRI is more effective than genomic biomarkers in determining his risk of adverse pathology/clinical features

4. A healthy 62-year-old man has an elevated PSA of 5.2 ng/dl and a firm nodule at the left base of the prostate on digital rectal examination. A transrectal ultrasound guided biopsy reveals 2 cores of grade group 3 disease. During counseling he inquires about possible further testing regarding prognosis for his cancer. The next step is to advise him that
   a. further testing is not needed
   b. preoperative testing of his biomarkers will assess his viability for possible active surveillance
   c. if organ-confined disease is diagnosed following radical prostatectomy, further testing may aid in decision making for possible adjuvant treatment
   d. if adverse pathology is diagnosed following radical prostatectomy, further testing may aid in decision making for possible adjuvant treatment

5. A healthy 66-year-old man with a family history of prostate cancer has an elevated PSA of 6.2 ng/dl, which increased from 3.2 ng/dl the previous year. A repeat PSA confirms persistent elevation, and digital rectal examination reveals a 30-gm gland without a discreet nodule. He undergoes transrectal ultrasound guided biopsy, which reveals no cancer. Previous attempts to obtain an MRI were denied by his insurance carrier. During counseling the patient states he is concerned that he may still have cancer, but he cannot afford the out-of-pocket costs for an MRI and he will not undergo a repeat biopsy unless deemed absolutely necessary. The next step is
   a. saturation biopsy
   b. MRI with fusion biopsy
   c. ConfirmMDx assay
   d. repeat PSA and digital rectal examination in 6–12 months

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