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NCCN Guidelines Panel: Prostate Cancer Treatment

On behalf of Myriad Genetic Laboratories, Inc., I respectfully request the NCCN Prostate Cancer Panel to review the enclosed data in support of modifications to the way in which tumor-based molecular assays are presented within the guidelines.

Specific changes:

1. On page PROS-1, add the following statement as a distinct step immediately to the right of "Life expectancy >5 years[b] or symptomatic" (see attached schematic example):

   "Tumor-based molecular assay[c] if therapeutic decisions would be altered by estimating:
   - ***prostate cancer-specific mortality***
   - ***metastasis-free survival***
   - ***risk of surgical findings showing adverse pathology"***

2. Modify footnote "c" as shown below. Tumor-based molecular assays for prostate cancer have been validated in a wide variety of study designs, therefore removal of "case-cohort" would be a more accurate description of the evidence base.

   "~~Men with clinically localized disease may consider the use of tumor-based molecular assays.~~
   Retrospective ***~~case cohort~~*** *studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN 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 of salvage radiotherapy."*

3. On page MS-46, modify the Prolaris content in Table 1 as follows:

   - Add the following row to reflect the patient population in the recently published Koch et al.[8] publication described under "Rationale" below.

Populations Studied	Outcome Reported (Test independently predicts)
RP and salvage radiation	Biochemical recurrence and metastasis

- Modify the following statement in the column "MolDX Recommendations", based on the recently finalized coverage determination, "MolDX: Prolaris Prostate Cancer Genomic Assay for Men with Favorable Intermediate Risk Disease L37043".

  *"Cover post-biopsy for NCCN very low-, **~~and~~** low-, **and favorable intermediate**-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy.*

FDA Clearance: At this time, the FDA has chosen to exercise its "enforcement discretion" over Laboratory Developed Tests (LDTs). LDTs are routinely performed based on the Clinical Laboratory Improvement Amendment (CLIA) and College of American Pathologists (CAP) certification, without FDA premarket approval or clearance.

Rationale: Since the first mention of tumor-based molecular assays in the 2015 NCCN Prostate Cancer guidelines, additional data has been published in support of the Prolaris® test, a 46-gene RNA-expression assay that directly measures tumor cell growth characteristics to generate a cell-cycle progression (CCP) score. In eight published studies, comprised of 10 separate cohorts of more than 2,900 patients, the CCP score proved to be an independent and the most powerful variable in predicting the risk of prostate cancer progression, as determined by the clinically meaningful oncologic endpoints of biochemical recurrence, prostate cancer-specific mortality, and metastasis. [1-8]

- Tosoain et al. [7] assessed men who underwent radical prostatectomy for Gleason score ≤6 prostate cancer. Prolaris added significantly to the prediction of biochemical recurrence in multivariate analysis, both in the overall cohort and in the subset of men meeting NCCN low risk criteria.
- Koch et al.[8] evaluated CCP score discrimination between systemic disease and local recurrence in patients with biochemical recurrence after radical prostatectomy. The CCP score was found to be a significant predictor of systemic disease (p=0.0060).
- A second validation study demonstrating that Prolaris accurately predicts the 10-year risk of prostate cancer metastasis after definitive therapy was recently presented at the American Urological Association 2017 annual meeting. [9] Among 767 men with localized prostate cancer (40% of whom were African American), Prolaris was a significant predictor of metastatic disease (HR/unit score=2.76;p=2.8×10^{-11}), with no difference in predictive performance between races or treatment groups.

Given the existing published data and Medicare coverage for Prolaris and other prostate cancer prognostic tests, physicians have incorporated these tests into routine clinical practice. We recommend that the use of tumor-based molecular assays should be reflected in the treatment algorithm itself as part of initial clinical assessment, as opposed to being consigned to a footnote. We believe that this change will allow for improved access to such testing for appropriate patients.

Literature support: A list of all publications supporting the use of Prolaris to predict biochemical recurrence, prostate cancer-specific mortality, and metastasis is provided below.

Sincerely,

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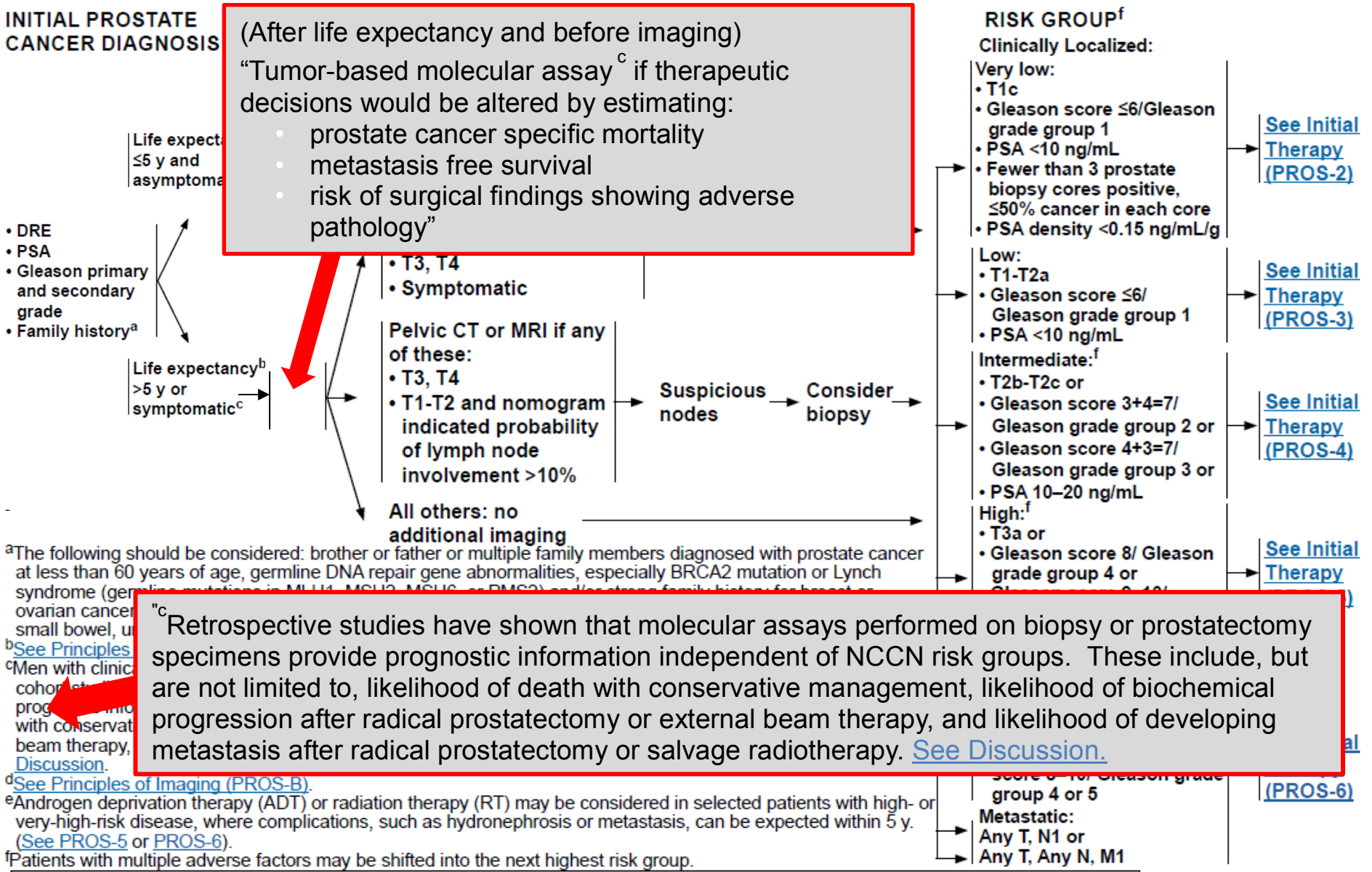
References:

1. Cuzick J, Swanson GP, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol*. 2011 Mar;12(3):245-55.
2. Cuzick J, Berney DM, Fisher G, et al. Transatlantic Prostate Group. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2012 Mar 13;106(6):1095-9.
3. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol*. 2013 Apr 10;31(11):1428-34.
4. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013 Aug 1;86(5):848-53.
5. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the CCP score generated from biopsy in men treated with prostatectomy. *J Urol* 2014 Aug; 192(2):409–14.
6. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2015; 113:382–9.
7. Tosoian JT, Chappidi MR, Bishoff JT, et al. Prognostic utility of biopsy-derived cell cycle progression score in patients with NCCN low-risk prostate cancer undergoing radical prostatectomy: implications for treatment guidance. BJU Int. 2017 May 8. doi: 10.1111/bju.13911. [Epub ahead of print] PubMed PMID: 28481440.
8. Koch MO, Cho JS, Kaimakliotis HZ, et al. Use of the cell cycle progression (CCP) score for predicting systemic disease and response to radiation of biochemical recurrence. Cancer Biomark. 2016 Jun 7;17(1):83-8.
9. Bardot et al. . Comparing the prognostic utility of the CCP score for predicting metastatic disease in African American and Non-African American men with prostate cancer. Presented at American Urological Association annual meeting, May 2017.

(After life expectancy and before imaging)
"Tumor-based molecular assay [c] if therapeutic decisions would be altered by estimating:
- prostate cancer specific mortality
- metastasis free survival
- risk of surgical findings showing adverse pathology"



[a] The following should be considered: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age, germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (ger… ovarian cancer… small bowel, u…

[b] See Principles…

[c] Men with clinic… cohor… prog… with conservat… beam therapy, … Discussion.

"[c] Retrospective studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN 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 radiotherapy. See Discussion.

[d] See Principles of Imaging (PROS-B).

[e] Androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered in selected patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastasis, can be expected within 5 y. (See PROS-5 or PROS-6).

[f] Patients with multiple adverse factors may be shifted into the next highest risk group.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.