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NCCN Guidelines Panel: Prostate Cancer

On behalf of GenomeDx Biosciences, we respectfully request the NCCN Prostate Cancer Guidelines Panel to review the enclosed data in support for inclusion of the 22-marker genomic classifier (GC) tumor tissue-based molecular assay (Decipher® Prostate Cancer Classifier) in the NCCN clinical practice guidelines for localized prostate cancer. The Decipher GC has demonstrated, across multiple studies, the ability to provide accurate predictions of important clinical endpoints such as biochemical failure, metastasis and prostate cancer-specific mortality when assessed from initial prostate needle biopsy or surgical specimens. Specifically, the strongest evidence of the clinical utility of Decipher is based on surgical cohorts of men with adverse pathology at radical prostatectomy or upon PSA rise/biochemical recurrence (see citations below). Discussion of Decipher is currently included in the current version of the NCCN guidelines in Table 1 on page MS-40 (Version 2.2016), and we appreciate the NCCN's consideration of these additional modifications.

**Specific Changes**:

On PROS-2, PROS-3, PROS-4, and PROS-5 of NCCN V2.2016, we recommend adding the sentence **"The 22-marker genomic classifier assay can be considered in men with one or more adverse laboratory/pathologic features or biochemical recurrence to guide the use of treatment such as adjuvant or salvage radiotherapy after radical prostatectomy."** as an additional footnote to term "Adverse features" next to footnote "j".

On PROS-7 of NCCN V2.2016, we recommend adding the sentence **"The 22-marker genomic classifier assay can be considered in men with one or more adverse laboratory/pathologic features or biochemical recurrence to guide the use of treatment such as adjuvant or salvage radiotherapy after radical prostatectomy."** as a footnote to term "Studies negative for distant metastases".

**FDA Clearance**:

Performance of Decipher Prostate Cancer Classifier is regulated and certified as a laboratory developed test under the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP). FDA clearance is not required for this assay.

**Rationale**:

The Decipher 22-marker GC assay has been validated as an independent predictor of biochemical failure, metastasis and prostate cancer specific death in over 2,700 patients from 10 multi-institutional cohorts of men treated for prostate cancer with radical prostatectomy in both academic and community based practice settings as reported in over 23 peer-reviewed publications. Decipher is covered by Centers for Medicare & Medicaid Services (CMS) for Medicare patients eligible for post-operative radiation therapy[1].

- The GC assay has been shown to consistently outperform or add to standard of care clinico-pathological variables as a means to better risk stratify prostate cancer disease[2-16].
- Multiple studies have shown how GC can predict necessity of adjuvant/early salvage radiotherapy and identify men who may be optimally managed with observation after initial local therapy[12-16].
- The GC assay increases concordance between urologist and radiation oncologist treatment decisions, and in prospective utility studies to not only change post-operative treatment in a third of men but also demonstrate improvements to health-related quality of life[17-23].

**Citation of literature (selected):**

**Studies demonstrating superior performance of Decipher for predicting survival after radical prostatectomy using initial diagnostic biopsy or surgical specimens:**

1. Local Coverage Determination (LCD): MolDX-CDD: DECIPHER® Prostate Cancer Classifier Assay (L36345) – ***Decipher is covered for Medicare beneficiaries to enhance risk stratification and measure the risk of metastasis in prostate cancer patients who have pathological stage T2 with a positive surgical margin or pathological stage T3 disease or rising PSA.***
2. Erho N, et al., Discovery and Validation of a Prostate Cancer Genomic Classifier that Predicts Early Metastasis Following Radical Prostatectomy. PLoS ONE 2013; 8(6):e66855. – ***Decipher predicts metastasis post-radical prostatectomy (RP) independent of clinical risk factors in multivariable analysis adjusting for standard of care clinico-pathological risk factors***

3. Karnes RJ, et al., Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population. The Journal of Urology 2013; 190:2047-2053. – ***98% of the Decipher low-risk patients (60% of the cohort) showed 5-year metastasis free survival despite post-RP adverse pathologic features and approximately 10-fold lower risk than Decipher high-risk patients treated at the Mayo Clinic. Results show that even after adjusting for clinico-pathological risk factors in multivariable analysis, Decipher provides independent prediction of metastasis and improved risk stratification.***
4. Klein, E. et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. European Urology 2015; 67(4): 778-786. **– *Decipher improves accuracy of standard risk-stratification tools (CAPRA-S and Stephenson nomogram) in predicting metastatic disease within 5 years in men with adverse pathologic features after surgery who received no adjuvant therapy. Patients with low-risk Decipher score had 95% metastasis-free survival at 5 years. Results highlight that despite presence of adverse pathology and lack of adjuvant radiotherapy good prostate cancer survival outcomes for the majority of the population with Decipher low risk scores are achievable with surgery alone.***
5. Cooperberg et al., Combined Value of Validated Clinical and Genomic Risk Stratification Tools for Predicting Prostate Cancer Mortality in a High-risk Prostatectomy Cohort. European Urology 2015; 67(2): 326-333. – ***Decipher predicts prostate cancer specific mortality (PCSM) after surgery. For Decipher high-risk patients, the cumulative incidence of PCSM was 45% at 10 years, whereas Decipher low-risk patients had 99% PCSM free survival even after adjusting for use of adjuvant therapy in this cohort****.*
6. Prensner, J.R. et al., RNA biomarkers associate with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. Lancet Oncol, 2014; 15(13): p. 1469-80. – ***Decipher outperforms (AUC 0.77) compared to CAPRA-S clinical risk model (AUC 0.69) in a pooled analysis of 1,008 RP patients from multiple cohorts.***
7. Yamoah et al. A novel biomarker signature, which may predict aggressive disease in African-American men with prostate cancer. *Journal of Clinical Oncology 2015;* doi: 10.1200/JCO.2014.59.8912. – ***Decipher was validated to predict metastasis within 5 years post radical prostatectomy in both African American and European American men with discriminatory accuracy (c-index) of 0.78 and 0.88, respectively. Results show comparable performance of Decipher in men with prostate cancer of African and of European descent****.*
8. Ross et al. Tissue Based Genomics Augment Post-Prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. European Urology. 2016 Jan; 69(1): 157-65. – ***Decipher is validated for predicting metastasis free survival at 10 years in a natural history cohort of intermediate and high risk men treated with surgery but without additional treatment until metastatic onset. Decipher provided significant improvement to the prognostic performance of validated models (Eggener's risk model and CAPRA-S) and pathologic risk factors. Results show that the majority of men with adverse pathology but low Decipher risk have excellent survival outcomes even without any adjuvant or salvage therapy.***
9. Glass et al. Validation of a genomic classifier for predicting post-prostatectomy recurrence in a community-based healthcare setting. Journal of Urology 2016; doi: 10.1016/j.juro.2015.11.044. – ***Decipher was validated to predict metastasis for men with high risk prostate cancer treated in community hospital setting. The discriminatory accuracy (c-index) was 0.74 for CAPRA-S, 0.80 for Decipher and 0.84 for the combined Decipher and CAPRA-S model. Results show Decipher predicts multiple survival endpoints in men treated in the community similar to that observed in tertiary referral settings.***
10. Klein et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. Urology 2016; Apr;90:148-52. – ***Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. Decipher predicted 5 and 10-year metastasis from genomic analysis of prostate needle-biopsy specimens with discriminatory accuracy (c-index) of 0.87 and 0.80, respectively.***
11. Knudsen et al. Application of a Clinical Whole-Transcriptome Assay for Staging and Prognosis of Prostate Cancer Diagnosed in Needle Core Biopsy Specimens. Journal of Molecular Diagnostics 2016; May:18(3): 395-406 – ***95% of transcriptomic features detected in RP specimens were detectable in biopsy tissues and demonstrated a high correlation (r=0.96). 75% of matched biopsy and RP pairs showed concordant molecular subtypes. Results show Decipher and genome-wide expression analysis may be performed from initial diagnostic biopsy or surgical specimens.***
12. Lee et al. Evaluation of a Genomic Classifier in Radical Prostatectomy Patients with Lymph Node Metastasis. Research and Reports in Urology, 2016 *in press*. – ***Decipher high risk patients had an 8-fold higher odds ratio of harbouring lymph node positive disease as compared to Decipher low risk patients. Results show Decipher scores were highly concordant between pre- and post-surgical specimens and Decipher scores from RP tissue were predictive of lymph node involvement (LNI) at RP.***

### Studies demonstrating utility of Decipher in the adjuvant and salvage settings:

13. Den et al., Genomic Prostate Cancer Classifier Predicts Biochemical Failure and Metastases in Patients After Postoperative Radiation Therapy. Int J Radiat Oncol Biol Phys 2014; 89(5):1038-46. – ***Decipher predicts distant metastasis after postoperative radiotherapy. Patients with high Decipher risk who received early radiation had 3% metastasis at 8 years vs. 23% for patients that got treated with late radiation.***
14. Den et al. A genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. Journal of Clinical Oncology 2015; 33:944-951. – ***Decipher predicts distant metastasis after postoperative radiotherapy. Decipher high-risk patients benefited from adjuvant radiation, demonstrating an 80% reduction in metastasis risk compared to those Decipher high-risk patients who delayed treatment and received salvage radiation. Demonstrates how Decipher may be used to optimally stratify patients into higher risk category that may benefit the most from early radiotherapy vs lower risk category that has excellent***

***outcomes with surgery and who may be salvaged if necessary without loss of oncologic benefits of earlier multi-modal therapy***


15. Ross et al. Efficacy of post-operative radiation in a prostatectomy cohort adjusted for clinical and genomic risk. Prostate Cancer Prostatic Disease 2016; May 3. doi: 10.1038/pcan.2016.15. - ***Both CAPRA-S and Decipher had independent predictive value on multivariable for metastasis (P<0.05). Men with low-to-intermediate CAPRA-S and low Decipher score have a low rate of metastatic events regardless of treatment selection. In contrast, men with high CAPRA-S and Decipher score benefit from adjuvant and salvage radiation.***
16. Ross AE, et al., A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate cancer and prostatic diseases 2014; 17(1): 64-9. – ***Decipher predicts regional and distant metastasis after biochemical recurrence outperforming PSA doubling time, the current best surrogate for disease recurrence.***
17. Freedland et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. European Urology 2016; doi: 10.1016/j.eururo.2016.01.008. – ***Decipher predicts metastasis following postoperative salvage radiation therapy. In patients treated with salvage radiotherapy (SRT) for PSA recurrence, Decipher is a powerful predictor of metastasis. Patients with low Decipher risk had good outcomes even with SRT alone. Patients with high Decipher risk are at highest risk for metastatic disease and SRT failure and may benefit from intensification of the therapy beyond SRT.***


**Studies demonstrating impact of Decipher on clinical decision making for urologists and radiation oncologists:**


18. Lobo et al., Evaluating clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. PLoS One. 2015;10(3):e0116866. – ***Decision analytic modeling shows compared to 'usual care', Decipher individualized estimates of risk result in an 18% absolute increase in 5- and 10-year metastasis-free survival in two populations.***
19. Michalopoulos et al., Influence of a genomic classifier on post-operative treatment decisions in high-risk prostate cancer patients: results from the PRO-ACT study. Curr Med Res Opin 2014; 30(8):1547-56. – ***Study shows 32% change in patient management by academic and community-based users of Decipher.***
20. Badani et al., Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. British Journal of Urology Intl 2014; 115(3): 419-429. – ***Study shows 31% change in patient management using Decipher for consecutive high-risk patients managed in community-based practice.***
21. Nguyen, P., et al., Impact of a Genomic Classifier of Metastatic Risk on Post-Prostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. Urology 2015 Jul; 86(1): 35-40. – ***Decipher test results significantly influenced adjuvant post-surgery treatment recommendations, reducing disagreement between urology and radiation oncology practice specialties in their management of men with adverse pathology or biochemical recurrence.***
22. Badani et al., Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group. Oncotarget 2013; 4(4): 600-9. – ***43% of urologists changed recommendations in the adjuvant and 53% of urologist changes treatment recommendations in the salvage setting.***
23. Gore et al., Effect of a genomic classifier on adjuvant treatment decision-making among patients with high-risk pathology at radical prostatectomy: Results from the multicenter prospective PRO-IMPACT study. J Clin Oncol 34, 2016 (suppl; abstr 5053). – ***18% of treatments changed, including 9% of low-risk and 31% of high-risk patients. Knowledge of Decipher results was associated with treatment decision-making among these patients: patients at low risk for metastasis had higher rates of observation and patients at high risk had higher rates of adjuvant radiotherapy. Decision quality was improved for patients exposed to Decipher results. This is the first report from a pre-planned interim analysis of a prospective clinical trial of Decipher demonstrating it's positive impact on patient management and health-related quality of life***.
24. Gore et al., Effect of a genomic classifier on treatment decision-making among patients with biochemical recurrence after radical prostatectomy: Results from the multicenter prospective PRO-IMPACT study. J Clin Oncol 34, 2016 (suppl; abstr e16558). **– *39% of management recommendations changed post-GC, including 29% of GC low-risk patients and 65% of GC high-risk patients. Knowledge of GC results was associated with treatment decision-making among patients with recurrence after RP. Patients found to be low risk for metastases by GC had higher rates of observation recommendations and patients at high risk had higher rates of salvage radiotherapy (SRT) in combination with hormone therapy treatment. Decision quality was improved among patients considering SRT after RP exposed to GC.***


Sincerely,


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