Submitted by: Chief Scientific Officer
Name: Elai Davicioni
Company/Organization: GenomeDx Biosciences Inc.
Address: 10355 Science Center Drive
Email: elai@genomedx.com
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NCCN Guidelines Panel: Prostate Cancer

On behalf of GenomeDx Biosciences, we provide an overview of the GenomeDx Decipher assay and respectfully request the NCCN Prostate Cancer Guidelines Panel to review the enclosed data in support for inclusion of additional data for the tumor tissue-based molecular assay (Decipher®) in the NCCN clinical practice guidelines for localized prostate cancer. The Decipher genomic classifier (GC) has demonstrated, across multiple studies, the ability to provide accurate predictions of important clinical endpoints such as prostate cancer-specific mortality, metastasis and biochemical recurrence when assessed from initial prostate needle biopsy or surgical specimens. In particular, Decipher can provide additional prognostic risk stratification within categories of established NCCN clinical risk groups or nomograms such as CAPRA-S. Decipher is currently included in the current version of the NCCN guidelines in PROS-2, PROS-3 and PROS-11 (Version 2.2018), and we appreciate the NCCN's consideration of these additional modifications.

Overview of Decipher:

The ability to obtain complete molecular information from small samples of routinely collected pathological tissue is beginning to revolutionize how we diagnose, classify and treat malignancies. GenomeDx Biosciences was founded on the premise of bringing clinically actionable genomic information to clinicians and patients. The Decipher product represents a CLIA and CAP certified, whole genome microarray covering 1.4 million probes, with which expression of coding and non-coding RNAs is measured. On this platform, many molecular signatures are developed, validated and calibrated. The most thoroughly evaluated signature on this platform is the Decipher Genomic Classifier (GC), which is a prognostic signature of prostate cancer metastasis risk, now evaluated in several dozen studies and in prospective clinical utility trials. The majority of this letter and our requests to the NCCN relate to this genomic signature. Recent publications have described predictive signatures and molecular subtype classifiers of prostate cancer developed on the Decipher platform and available when Decipher is ordered on biopsy tissue or radical prostatectomy specimen [15-17]. These signatures describe patients with increased response to radiation therapy, benefit from adjuvant hormonal therapy and also can classify prostate cancer into luminal (more androgen receptor driven) and basal subtypes. We include information regarding these signatures in this document as well, however will await further independent validation prior to request for guideline inclusion.

Specific Changes Requested:

Request 1: We recommend modification to PROS 2-11 as described below.

PROS-2 The guidelines do not recommend the use of gene expression testing for unfavorable intermediate or high risk prostate cancer. However, the recently developed and validated clinical-genomic risk groups incorporating NCCN and Decipher risk groups using an easy to use summation method significantly improves risk stratification for these men [11] and can alter management decisions. Combining NCCN-Decipher has been shown to reclassify about 2/3 of patients staged by NCCN risk groups in a prospective analysis of nearly 6,000 patients. For example, among NCCN unfavorable intermediate risk patients 35% were reclassified to a lower risk tier with low rates of metastasis comparable to NCCN favorable intermediate risk patients. In addition, about 41% of NCCN unfavorable intermediate risk patients were reclassified to a higher risk tier with metastatic event rates similar to NCCN high risk patients. In a study of unfavorable intermediate risk men treated in a Canadian Phase II single-arm clinical trial of image-guided IMRT without any hormonal

manipulation, researchers found about 70% of men had low risk Decipher scores with <5% experienced biochemical failure and 0% metastasis at 5 years [12]. Finally, a study of NCCN intermediate and high risk patients treated with radiation and 4-6 months of ADT showed no metastatic events at 5 years among men with low Decipher risk scores [13, 14]. Therefore, Decipher can stratify this population beyond NCCN risk groupings and may be a consideration to guide hormone therapy use for patients being treated with definitive radiotherapy. This is similar to recent adoption by NCCN of the Zumsteg and Spratt et al., 2013 favorable/unfavorable intermediate risk sub-stratification. Based on retrospective analyses the researchers were able to show favorable intermediate risk did not benefit from additional ADT (see Appendix Figure 1).

PROS-3, footnote L: Decipher has been shown to predict for prostate cancer-specific mortality and distant metastasis after initial biopsy for patients treated with radiotherapy or surgery, independent of clinical risk models such as NCCN or CAPRA. Please add this to the statement which currently only mentions this for patients after prostatectomy [7] (see Appendix Figure 2).

PROS-4 – PROS-8: When considering adjuvant therapy after prostatectomy, given the relatively high number needed to treat (NNT) to prevent metastasis seen in randomized controlled studies (NNT=12[1]), we contend that individualized risk assessment and shared decision making should be employed. In PROS-4 through 8, when adverse pathological features are present after prostatectomy we suggest the inclusion of bullet points to calculate nomogram predictors of clinical or biochemical progression (i.e. CAPRA-S which has been validated in this setting) and additionally a bullet point for the Decipher as an independent prognostic marker that can augment the accuracy of these nomograms [1-7, 18-35], can reduce NNT to 3 [4] and can help decrease decision uncertainty and patient anxiety [6] (see Appendix Figure 3). The main body of evidence in over 1,600 unique patients with adverse pathology after RP from 10 multi-institutional cohort studies shows the following:

1) Decipher has improved discriminatory performance compared to clinical and pathological factors for predicting prostate cancer mortality, metastasis and biochemical failure

2) Decipher consistently shows significant association to prostate cancer mortality, metastasis and biochemical failure compared to other clinical and pathological factors tested

3) Decipher low and average risk patients had lower likelihood of recurrence or death as compared to Decipher high risk patients, who likely require adjuvant therapy.

PROS-11: Reference to be added: Among men with persistent PSA after prostatectomy Decipher has been shown to accurately reclassify risk and predict metastatic outcomes [7]. Decipher low and average risk patients had favorable outcomes as compared to Decipher high risk patients, who likely require intensification with systemic therapies (see Appendix Figure 4).

PROS-D 2 OF 3: For patients considering radiation therapy in PROS-D 2 OF 3, we suggest the addition to footnote 2 stating that "Decipher assay can be considered to provide an additional independent measure of metastasis risk." [12-14] (see Appendix Figure 5).

PROS-D 3 OF 3: For patients considering post-prostatectomy radiation therapy in PROS-D 3 OF 3, we suggest adding the statement, "Men with adverse risk features after RP may consider the use of Decipher. Retrospective studies have shown that Decipher performed on RP specimens provides likelihood of prostate cancer-specific mortality, metastasis and biochemical failure." [1-7, 18-35] (see Appendix Figure 6).

Request 2: We recommend adding the additional data as indicated below in red to Table 1 on page MS-47 (Version 2.2018).

Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis

[1] Thompson IM, Tangen CM, Paradelo MD, et al. JAMA. 2016; 296:2329-2335

Test	Platform	Populations studied	Outcomes Reported (Test Independently predicts)	References	Molecular Diagnostic Services Program (MolDx) Recommendations
Decipher	Whole-transcriptome 1.4 RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	Metastasis (GC) Prostate cancer-specific Mortality (GC) Post operative Radiation Sensitivity (PORTOS), Luminal or Basal Subtype, or ADT Response Signature (ADT-RS)	110, 415-424, ***Additional references provided below [1-17]***	Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir) Cover post-biopsy for NCCN very-low- and low-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
		Post RP, biochemical recurrence	Metastasis (GC) Prostate cancer-specific Mortality (GC) Post operative Radiation Sensitivity (PORTOS), Luminal or Basal Subtype, or ADT Response Signature (ADT-RS)		
		Post RP, adjuvant or salvage radiotherapy	Metastasis (GC) Prostate cancer-specific Mortality (GC) Post operative Radiation Sensitivity (PORTOS), Luminal or Basal Subtype or ADT Response Signature (ADT-RS)		
		Biopsy, localized prostate cancer treated with RP or EBRT	Metastasis (GC) Prostate cancer-specific Mortality (GC), Gleason grade 4 or higher disease at RP		

Note: Only sections of the table regarding Decipher are shown. Newly recommended additions are highlighted in red. GC refers to the Decipher Genomic Classifier [1-11, 14-31]. PORTOS refers to the 24 gene Post Operative Radiation Therapy Outcomes Score [15]. Luminal and Basal Subtypes refer to the 50 gene PAM50 subtype classifier [16]. ADT-RS refers to the 84 gene ADT Response Signature [17]. All signatures are available with the Decipher assay.

FDA Clearance:

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

Rationale:

Since the publication of NCCN Prostate Cancer Guidelines, Version 2.2018, there has been a number of new validation and clinical utility studies published for the Decipher GC assay. The new extended data further validates the Decipher prostate cancer GC as an independent predictor of biochemical failure, metastasis and prostate cancer specific death in both academic and community based practice settings from both initial prostate needle biopsy or surgical specimens. In summary, the Decipher assay has been validated in over 2,500 unique patients from over 10 multi-institutional cohorts of men treated for prostate cancer with radical prostatectomy as reported in over 30 peer-reviewed publications and in over 250 patients in 3 publications treated with primary radiation therapy (with or without concomitant androgen deprivation).

Citation of literature (selected):

*Additional Clinical Validation and Clinical Utility Studies for Decipher Prostate RP:

1. 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.
2. 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.*

3. Karnes R.J. et al. Validation of a genomic risk classifier to predict prostate cancer specific mortality in men with adverse pathologic features. *European Urology*. 2017. doi: 10.1016/j.eururo.2017.03.036.
4. Dalela D. et al. Genomic Classifier augments the role of pathological features in identifying optimal candidates for adjuvant radiation therapy in patients with prostate cancer: Development and internal validation of a multivariable prognostic model. *Journal of Clinical Oncology*. 2017. doi: 10.1200/JCO.2016.69.9918.
5. Spratt D.E. et al. Individual Patient Level Meta-analysis of the Performance of the Decipher Genomic Classifier in High Risk Men Post Prostatectomy to Predict Development of Metastatic Disease. *Journal of Clinical Oncology*. 2017. doi: 10.1200/JCO.2016.70.2811.
6. Gore J.L. et al., Decipher Test Impacts Decision-Making among Patients Considering Adjuvant and Salvage Treatment following Radical Prostatectomy: Interim Results from the Multicenter Prospective PRO-IMPACT Study. *Cancer*. 2017. doi: 10.1002/cncr.30665.
7. Spratt D.E. et al. . Performance of a Prostate Cancer Genomic Classifier in Predicting Metastasis in Men with Prostate-specific Antigen Persistence Postprostatectomy. *European Urology*. 2018. doi.org/10.1016/j.eururo.2017.11.024.

* Additional Clinical Validation and Clinical Utility Studies for Decipher Prostate Biopsy:

8. Klein et al. Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. *Urology*. 2016; Apr;90:148-52.
9. 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
10. Lee H.J. et al. Evaluation of a Genomic Classifier in Radical Prostatectomy Patients with Lymph Node Metastasis. Research and Reports in *Urology*. 2016 Jun; 8:77-84. doi: 10.2147/RRU.S99997
11. Spratt D.E. et al. Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. Journal of Clinical Oncology. 2018. doi.org/10.1200/JCO.2017. 74.2940.
12. Chua M. et al. A biopsy-based genomic classifier to predict biochemical failure after definitive radiation without hormone therapy in a prospective cohort of intermediate risk prostate cancer. 2018. *Journal of Clinical Oncology* 36, no. 6_suppl (February 20 2018) 68-68. DOI: 10.1200/JCO.2018.36.6_suppl.68
13. Nguyen P.L. et al. Utilization of Biopsy-based Genomic Classifier to Predict Distant Metastasis after Definitive Radiation and Short-Course ADT for Intermediate and High Risk Prostate Cancer. *Prostate Cancer Prostatic Dis*. 2017. Jan; doi: 10.1038/pcan.2016.58.
14. Nguyen P.L. et al. Ability of a genomic classifier to predict metastasis and prostate cancer-specific mortality after radiation or surgery based on needle biopsy specimens. *European Urology*. 2017. doi: 10.1016/j.eururo.2017.05.009.

* Studies Describing Additional Signatures Available with the Decipher Assay:

15. Zhao S.G. et al. The Development and Validation of a 24-gene Predictor of Response to Post-operative Radiation Therapy in Prostate Cancer: A Matched Retrospective Analysis. *Lancet Oncology*. 2016 Nov; 17(11):1612-1620 – **Defined and validated a 24 gene signature predicting post operative response to radiation therapy (PORTOS). This signature was not prognostic of outcome in men not treated with post-operative radiation, however in men treated with post operative radiation, tumors from men with high PORTOS scores demonstrated a 7 fold improved metastasis free survival when compared to men with low PORTOS scores**
16. Zhao S.G. et al. Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. *JAMA Oncology*. 2017. doi: 10.1001/jamaoncol.2017.0751 – **Defined and validated a micro-arry derived PAM50 classifier which groups prostate cancer into luminal A, luminal B and basal subtypes, similar to groupings defined in breast cancer. Luminal subtypes demonstrated increased expression of canonical androgen responsive genes and luminal B tumors (when compared to non-luminal B subtypes) had improved oncological outcomes when androgen deprivation therapy was employed in the post operative setting.**
17. Karnes R.J. et al. Development and validation of a prostate cancer genomic signature that predicts early ADT treatment response following radical prostatectomy. *Clinical Cancer Research*. 2018 doi: 10.1158/1078-0432.CCR-17-2745 – **An ADT Response Signature (ADT-RS) was identified from neuroendocrine and AR-signaling related genes. Patients with high ADT-RS benefited from adjuvant ADT**.

Studies demonstrating superior performance of Decipher for predicting survival and clinical efficacy post-RP:

18. 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.
19. Karnes RJ, et al. Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population. *Journal of Urology*. 2013; 190:2047-2053.
20. 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.

21. 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.
22. 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.
23. 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.
24. Ross AE, 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.
25. Klein EA, et al. Molecular analysis of low grade prostate cancer using a genomic classifier of metastatic potential. *Journal of Urology* 2017;197:122-128.

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

26. 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.
27. 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.
28. 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.
29. 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.

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

30. Lobo J.M, et al. Cost effectiveness of the Decipher genomic classifier to guide individualized decisions for early radiation therapy after prostatectomy for prostate cancer. *Clinical Genitourinary Cancer*. 2017. Jun;15(3):e299-e309
31. Lobo et al. Evaluating clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. *PLoS One*. 2015;10(3):e0116866.
32. 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.
33. 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.
34. 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.
35. 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.

Sincerely,

Elai Davicioni, PhD
President & Chief Scientific Officer
GenomeDx Biosciences
San Diego, CA