

Submitted by: Chief Scientific Officer

Name: Elai Davicioni

Company/Organization: GenomeDx Biosciences Inc.

Address: 10355 Science Center Drive

Phone: 626-710-2695, Email: elai@genomedx.com

Date of request: June 01, 2017

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 biochemical failure, metastasis and prostate cancer-specific mortality when assessed from initial prostate needle biopsy or surgical specimens. In particular, Decipher can provide additional prognostic risk stratification within categories of established clinical risk groups or CAPRA-S. Discussion of Decipher is currently included in the current version of the NCCN guidelines in Table 1 on page MS-46 (Version 2.2017), 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 microarrays covering 1.4 million probes, with which expression of coding and non-coding RNAs is measured. On this platform, 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 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 [12,13]. These signatures describe patients with increased response to radiation 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 2-8 as described below.

1. In PROS-2 through PROS-6 when considering adjuvant therapy, given the relatively high number needed to treat (NNT) to prevent metastasis seen in randomized controlled studies (NNT=12¹), we contend that individualized risk assessment and shared decision making should be employed. In PROS-2 through 6, 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 GC as an independent prognostic marker that can augment the accuracy of these nomograms [1-6, 12-29], can reduce NNT to 3 [4] and can help decrease decision uncertainty and patient anxiety [6] (see appendix

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



Figure 1).

- For patients considering EBRT in PROS-3 and 4 we suggest the addition of a footnote stating that “Decipher assay can be considered to provide an additional independent measure of metastasis risk.” [9-11] (see Appendix Figures 2 and 3)
- In PROS-8, in addition to PSADT we suggest the addition of a bullet point for the Decipher GC as an independent predictor of metastatic progression in the setting of clinical M0 disease and a persistent or recurrent PSA after treatment (see appendix Figure 4). [20-23]

Request 2: We recommend adding the additional data as indicated below in red to Table 1 on page MS-46 (Version 2.2017).

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

Test	Platform	Populations studied	Outcomes Reported (Test Independently predicts)	References	Molecular Diagnostic Services Program (MoDx) 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	110, 415-424, <i>*Additional references provided below [1-13]</i>	Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis (GC) Prostate cancer-specific Mortality (GC) Post operative Radiation Sensitivity (PORTOS), Luminal or Basal Subtype		
		Post RP, adjuvant or salvage radiotherapy	Metastasis (GC) Prostate cancer-specific Mortality (GC) Post operative Radiation Sensitivity (PORTOS), Luminal or Basal Subtype		
		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 [12]. Luminal and Basal Subtypes refer to the 50 gene PAM50 subtype classifier [13]. 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) and the College of American Pathologists (CAP). FDA clearance is not required for this assay.

Rationale:

Since the publication of NCCN Prostate Cancer Guidelines, Version 2.2016, 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 2,700 patients from over 10 multi-institutional cohorts of men treated for prostate cancer with radical prostatectomy as reported in over 25 peer-reviewed publications and in over 130 patients in 2 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. – ***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.***
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. – ***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.***
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. – ***Prostate Cancer Classifier was an independent predictor of prostate cancer specific mortality beyond clinical-pathological features and existing nomograms. GC stratified the cumulative incidence of PCSM among men with adverse pathological features from 2.8% to 30%.***
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. – ***GC was among four independent risk factors (others included pT3b/pT4, N1, GG 4-5) which predicted increased benefit to adjuvant radiation therapy.***
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. – ***GC was independently prognostic of metastatic risk across all clinical and pathological subgroups of men with adverse pathology after radical prostatectomy.***
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. – ***In a prospective multi-institutional study, the Decipher GC reduced decision conflict and anxiety and caused changes in management decisions after radical prostatectomy***

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

7. 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 and Gleason grade 4 or higher disease at RP. Decipher predicted 5 and 10-year metastasis as well as high grade disease at RP from genomic analysis of prostate needle-biopsy specimens with discriminatory accuracy (c-index) of 0.87, 0.80 and 0.71 respectively.***
8. 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.***
9. 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 – ***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 LNI at RP***
10. 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. – ***In men undergoing primary radiation therapy, Decipher GC was the only significant predictor of future clinical progression on multi-variable analysis***
11. 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. – ***In a combined cohort of men undergoing RP or EBRT, Decipher independently predicted metastatic progression and prostate cancer specific mortality***

*** Studies Describing Additional Signatures Available with the Decipher Assay:**

12. 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***

GENOMEDX.COM

10355 Science Center Drive, Suite 240 San Diego, CA 92121

t 763.245.0620 f 855.324.2768



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

13. 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-array derived PSAM50 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.**

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

14. 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**
15. 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.**
16. 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.**
17. 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.**
18. 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.**
19. 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.**
20. 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. – **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.**
21. Klein EA, et al. Molecular analysis of low grade prostate cancer using a genomic classifier of metastatic potential. J Urol 2017;197:122-128. - **Of men with Gleason score (GS) 6 disease only, 80% had a low Decipher score, and the median Decipher score in the GS6 patients with adverse pathological features such as EPE and SVI was significantly higher.**

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

22. 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.**
23. 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.

24. 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.***
25. 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:

26. 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 – ***Decipher-guided patient management was found to be a cost-effective approach for genomics-driven treatment decisions after surgery when compared to usual care***
27. 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.***
28. 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.***
29. 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.***
30. 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.***
31. 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.***

Sincerely,

Ashley E. Ross, MD PhD
Chief Medical Advisor
GenomeDx Biosciences, Sandiego, CA

Bruce J. Trock, PhD
Professor of Urology, Epidemiology, Oncology, Environmental Health
Director, Division of Epidemiology
Johns Hopkins Medical Institutions

Elai Davicioni, PhD
President & CSO
GenomeDx Biosciences, San Diego, CA

