DECIPHER BIOSCIENCES

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NCCN Guidelines Panel: Prostate Cancer

On behalf of Decipher Biosciences, we 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 prostate cancer.

The Decipher genomic classifier (GC) has demonstrated the ability improve physician and patient decision making and alter treatment decisions in a prospective trial (PRO-IMPACT), improve the ability to better select patients for adjuvant radiotherapy or observation post-prostatectomy, guide androgen-deprivation therapy use in unfavorable intermediate risk prostate cancer from a prospective registry, and identify low risk patients most likely to experience a biochemical recurrence and may not be best suited for conservative management. Decipher was also recently validated in the SPARTAN randomized trial to risk stratify patients most likely to benefit from apalutamide, which found Decipher was highly prognostic.

Decipher consistently and significantly improves risk stratification over currently used clinical/pathological risk factors as well as risk models such as the NCCN or CAPRA risk groups. Decipher has consistently, and across multiple retrospective studies, demonstrated its ability to accurately predict important clinical endpoints such as biochemical failure, metastasis and prostate cancer-specific mortality when assessed from initial prostate needle biopsy or surgical specimens. Decipher has been incorporated prospectively as a stratification variable given it has been established as the strongest prognostic variable in prostate cancer and is included in prospective randomized trials (NCT02783950, NCT03070886). Additionally, given Decipher's robust data it is now being used to guide treatment selection in multiple randomized trials moving through ECOG and NRG Oncology. Thus, there is inconsistency in the level of evidence provided by Decipher, its foundational role in stratifying and guiding treatment selection in NCI-funded clinical trials, and the recommendations by NCCN. The data to support Decipher is more robust than MRI, molecular imaging, or germline testing in localized prostate cancer. We would request you closely review the extensive evidence to support Decipher testing as the level of evidence to support Decipher has risen far above the other commercial gene expression tests and should not be grouped together or held back given other tests lack of data. Decipher is currently included in the current version of the NCCN guidelines in PROS-2, PROS-3 and PROS-12 (Version 2.2019), and we appreciate the NCCN's consideration of these additional modifications.

Specific Changes Requested:

Request 1: PROS-2, NCCN low risk and favorable intermediate risk prostate cancer, change "consider if life expectancy >10 years" to "recommend if life expectancy > 10 years"

Request 2: PROS-2, NCCN unfavorable and high risk prostate cancer, change "not routinely recommended" to "recommend if life expectancy > 10 years"

Request 3: PROS-4 – PROS-8, footnote t "Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; or detectable PSA" change to "Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA or high genomic classifier score (GC>0.6)"

Request 4: PROS-12, footnote ll change "…Decipher molecular assay (category 2B) can be considered to inform counseling" to "Decipher molecular assay to further risk stratify and inform counseling"

Request 5: PROS-D, page 4 of 5, Post-Prostatectomy Radiation Therapy, change "The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSADT to individualize treatment discussion" to "The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT and Decipher molecular assay to individualize treatment discussion"

Request 6: We recommend adding the additional data as indicated below (highlighted in red) to Table 1 on MS-61.

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:

The guidelines recommend (not "consider") the use of germline genetic testing for localized prostate cancer based on retrospective data (e.g., The Cancer Genome Atlas) that have not demonstrated any meaningful clinical utility for men who already harbor early stage localized prostate cancer (as opposed to the at risk population). This contrasts with the evidence generated for the utility of gene expression-based prognostic biomarkers.

Furthermore, the guidelines do not recommend (or even "consider") gene expression testing for unfavorable intermediate or high risk prostate cancer. For example, Spratt et al., have demonstrated that addition of Decipher to the NCCN risk model would reclassify (or further risk stratify) 2/3 of men staged by NCCN risk groups in a prospective analysis of nearly 6,000 patients [8]. Berlin et al., in a prospective cohort found Decipher stratified 72% of unfavorable intermediate risk as low risk and found these men had a 95% 5-year biochemical failure-free and 100% 10-year metastasis-free survival when treated with external beam radiation therapy (EBRT) without any hormonal manipulation as primary therapy [9]. In addition, Nguyen et al., found unfavorable and high risk men with low Decipher risk scores treated with EBRT and 4-6 months of ADT had excellent outcomes (showed no metastatic events at 5 years) and could be considered for shorter durations than standard of care 18-24 months ADT [10, 11]. Therefore, Decipher can improve risk stratification of clinically localized disease beyond NCCN risk groupings. The guidelines for favorable intermediate risk (PROS-6) which allow for EBRT or brachytherapy alone as opposed to those for unfavorable intermediate risk (PROS-7) which recommend addition of 4-6 months of ADT were adopted by NCCN based on the Zumsteg and Spratt et al., 2013 risk model. This clinical risk model was developed and validated in retrospective analyses similar to those that have been conducted for the Decipher genomic risk model. Therefore, we request NCCN guidelines recommend gene-expression testing of tumor to further improve risk stratification for those diagnosed with intermediate and high risk clinical localized disease.

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

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

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assessment and shared decision making should be employed. Dalela et al., found that addition of high Decipher (GC>0.6) reduced the NNT to 3 [26] and Gore et al., found it can help decrease decision uncertainty and patient anxiety [31] in the adjuvant setting. For men with PSA persistence after radical prostatectomy (RP), Spratt et al., found Decipher to accurately reclassify risk and predict metastatic outcomes observing the Decipher low-intermediate risk groups had favorable outcomes with salvage EBRT alone as compared to Decipher high risk patients, who likely require intensification with systemic therapies [24].

Since the publication of NCCN Prostate Cancer Guidelines, Version 2.2019, there has been a number of new validation and clinical utility studies published for the Decipher GC assay. The data further validate the Decipher prostate cancer GC as an independent predictor of adverse pathology at RP, biochemical failure, metastasis and prostate cancer specific death in both academic and community-based practice settings from both initial prostate needle biopsy [1-11] or surgical specimens [12-29]. Decipher test results change practice management and the physician-patient shared decision for both urologists and radiation oncologists [30-37]. In addition, Decipher is highly correlated to other biomarkers of disease aggressiveness such as histologic grade and PI-RADS MRI score [38-42]. Finally, results from the SPARTAN randomized trial demonstrate the validity of tissue-based genomic testing with Decipher to predict metastasis-free survival even for men with castrate resistant disease [43]. In summary, the Decipher assay is a highly validated prognostic biomarker as demonstrated in >40 studies of over 5,000 unique patients with long-term follow up and outcomes [1-43].

Sincerely,

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Founder & Chief Scientific Officer

Bashar Dabbas MD
Chief Medical Officer & Medical Director

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

Test	Platform	Populations studied	Outcomes Reported (Test independently predicts)	References	Molecular Diagnostic Services Program (MolDx) Recommendations
Decipher	Whole-transcriptome expression assay (46,050 genes & non-coding RNA) oligonucleotide microarray optimized for FFPE tissue	Biopsy, localized prostate cancer treated with RP or EBRT	• Non-organ confined (pT3) or grade group 3 disease at RP [1-4] • lymph node metastasis [5-6] • biochemical failure/recurrence [9] • metastasis [7-11] • prostate cancer-specific mortality [8]	110, 415-424, ***Additional references provided***	Cover post-biopsy for NCCN very-low- and low-risk, NCCN favorable intermediate and unfavorable intermediate risk prostate cancer in patients with at least 10 years life expectancy who have not received prior treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post radical prostatectomy (RP), adverse pathology/high-risk features	• metastasis [12-20] • prostate cancer-specific mortality [21-22]		
		Post RP, biochemical recurrence/PSA persistence	• metastasis [20, 23-25] • prostate cancer-specific mortality [21]		
		Post RP, adjuvant or salvage radiotherapy	• metastasis [20, 25-29] • prostate cancer-specific mortality [21-22]		
		m0 castrate-resistant prostate cancer (CRPC)	• metastasis-free survival [43]		

Note: Only sections of the table regarding Decipher are shown. Newly recommended additions and references are highlighted in red.

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Citation of literature (selected):

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