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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 to support updated guideline recommendations for the tumor tissue-based molecular assay, Decipher®, in the NCCN clinical practice guidelines for prostate cancer.

NCCN has led the way in providing guidance for the use of biomarkers, imaging, and therapy across disease sites, as well as in differentiating the level of evidence and data to support these modalities. Decipher has been committed to partner with a wealth of academic trial groups (e.g. PRO-IMPACT trial, G-MINOR randomized trial), NCTN cooperative groups (e.g., RTOG/NRG 9601, ECOG 3805 CHAARTED trial), international trial groups (e.g., STAMPEDE), and industry trial groups (e.g., randomized trials SPARTAN and TITAN).

As described in a recently completed systematic review of the evidence for the Decipher genomic classifier (GC) by leaders across North America in biomarkers, many of whom are represented on NCCN, ASCO, and other guidelines:[1]

- Prospective evidence has demonstrated that Decipher improves physician and patient decision-making post-prostatectomy in both the adjuvant and salvage settings, and guides treatment decisions in prospective trials (e.g., randomized trials PRO-IMPACT and G-MINOR) as well as the numerous multicenter studies as outlined in the systematic review.[1] Decipher significantly and independently improved prognostication, discrimination, changed management, and identified patients who could forgo more intensive treatments (e.g., hormone therapy with salvage RT). Given the strong prognostic ability of Decipher, it has been mandated as a stratification variable in the ongoing randomized phase II/III NRG GU002 (RADD!) trial to ensure balance in both arms. Decipher was given level 1 evidence in this large systematic review in accordance with AUA and Simon criteria.
- The study also outlined the strength of data for Decipher biopsy in >10,000 patients from prospective registries. Decipher improves active surveillance utilization in low and intermediate risk prostate cancer, identifies men with unfavorable intermediate risk disease that can safely omit hormone therapy with RT, and identifies high risk men with low risk of developing distant metastasis. Based on the strength of this data, the NCI-funded cooperative group NRG has now adopted Decipher into essentially every trial, as it is the strongest prognostic factor demonstrated to date. Decipher is being used as an integral biomarker for the two parallel phase III trials of NCCN high risk men that comprise NRG GU009 (PREDICT-RT) and, similarly, in the soon-to-

open NRG GU010 (GUIDANCE) randomized phase III trials for NCCN intermediate risk men. In addition, ECOG-ACRIN has recently opened EA8183 (ERADICATE) for men after radical prostatectomy, which utilizes Decipher as an integral biomarker, as only patients with a Decipher high genomic classifier score (GC>0.6) will be included in the randomization.

- There is also now growing evidence from randomized trials of patients with advanced prostate cancer demonstrating the utility of Decipher. Patients included in the SPARTAN, TITAN, and CHAARTED phase III randomized trials have now all undergone Decipher testing. Findings from all three of these randomized trials have been presented at national meetings and, most recently, the SPARTAN trial has been accepted for publication in JAMA Oncology. Each trial consistently demonstrates that Decipher independently improves prognostication and can identify patients who need earlier treatment and intensification beyond ADT alone.

Based on the large amount of prospective and high-level evidence, as defined by the landmark Simon et al guidance on levels of biomarker evidence, there is inconsistency between the level of evidence provided by Decipher and its foundational role in stratifying and guiding treatment selection in NCI-funded clinical trials and the recommendations by NCCN.

Decipher is the ONLY biomarker with robust and growing reported clinical trials, post-hoc randomized phase III trials, and ongoing randomized trials. There should be indication to a greater level of recommendation and evidence compared to other biomarkers listed in NCCN which are limited to retrospective observational studies.

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 and held back, given that the other tests lack comparable data**. Decipher is currently included in the current version of the NCCN guidelines in PROS-2 (footnote J, described in PROS-2A, referenced in PROS-4-PROS-7), PROS-4-PROS-7 (footnote s, described in PROS-7A), PROS-11, and PROS-E (Version 2.2021), and we appreciate the NCCN's consideration of these additional modifications.

Specific Changes Requested:

Request 1: PROS-11, footnote jj- **Change** *"...Decipher molecular assay (category 2B) can be considered to inform counseling*" **to** "*Decipher molecular assay is* ***recommended*** *to further risk stratify and inform counseling.* ***Patients with high Decipher genomic classifier score (GC>0.6) tumors should be strongly considered for the addition of ADT to EBRT. Lower genomic risk tumors may be considered for omission of ADT***."[2]

Request 2: PROS-4–PROS-7, footnote r (described in PROS-7A)- Change "*Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; or detectable PSA*" **to** "*Adverse laboratory/pathologic features include: positive margin(s); seminal vesicle invasion; extracapsular extension; detectable PSA* ***or high Decipher genomic classifier score (GC>0.6)***."[3,4]

Request 3: PROS-4 – PROS-7, footnote s (described in PROS-7A)- **Add** "***Men with high Decipher genomic classifier score (GC>0.6) should be strongly considered for early EBRT (ideally when PSA<0.2 ng/mL)***."[5,6]

Request 4: PROS-4 – PROS-5, footnote m (described in PROS-7A)- **Add** *"**Men with NCCN low or favorable intermediate risk group disease with a low risk tumor-based molecular assay result should be strongly considered for active surveillance.**"*[7,8]

Request 5: 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 6: PROS-2, NCCN unfavorable and high risk prostate cancer- **Change** "*consider if life expectancy >10 years*" to "***recommend** if life expectancy > 10 years*"

Request 7: PROS-E, page 1 of 5, Definitive Radiation Therapy by Risk Group, Favorable intermediate risk **Change** "*…Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.*" **to** "*…Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments, **such as tumor-based molecular assays,** suggest aggressive tumor behavior.*"[9,10]

Request 8: PROS-E, 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. **Men with high Decipher genomic classifier scores (GC >0.6) should be strongly considered for earlier EBRT and addition of ADT when the opportunity for early EBRT has been missed***."

Request 9: PROS-G, page 2- **Change** "*…Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encourage to consider ADT earlier*" **to** "*Patients with a shorter PSADT (or a rapid PSA velocity), **or a high Decipher genomic risk score (GC>0.6),** and an otherwise long life expectancy should be encourage to consider ADT earlier.*"[11]

Request 10: PROS-G, page 3- **Change** "*…Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encourage to consider ADT earlier*" **to** "*Patients with a shorter PSADT (or a rapid PSA velocity), **or a high Decipher genomic risk score (GC>0.6),** and an otherwise long life expectancy should be encourage to consider ADT earlier.*"[11]

Request 11: CAT-1**- Add a table for tumor-based molecular assays such as the one developed in the NCCN Breast Cancer guideline** (see BINV-N page 1). This table ranks assays by their NCCN Category of Preference as well as their NCCN Category of Evidence and Consensus. We request listing Decipher as "Preferred" in the NCCN Category of Preference since it is the only assay that has been tested in the setting of protocol-driven studies such as the NRG/RTOG Phase III randomized trial RTOG 96-01 as well as being included in several prospective NCI-funded

Phase III randomized trials (e.g., NRG GU009, EA8183). **We request the panel differentiate assays based on their level of evidence.**

Request 12: PROS 7-A, footnote s- Remove ***"if not previously performed"*** *from "Decipher molecular assay is recommended to inform adjuvant treatment* ~~***if not previously performed***~~ *if adverse features are found post-RP."*

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:

Request 1: Feng et al. demonstrated in their analysis of the NRG/RTOG 96-01 phase III randomized trial that patients with higher Decipher genomic risk had substantial absolute improvement in oncologic and survival outcomes with addition hormonal therapy to salvage radiotherapy, whereas the lower genomic risk patients had minimal absolute clinical benefit (eg. 12-year improvement in metastasis-free outcomes was ~11% for higher vs 0.4% for lower genomic risk).[2]

Requests 2, 3 & 8: Spratt et al., demonstrated in a meta-analysis of 855 patients from 5 published studies that Decipher is the most significant predictor of metastasis after radical prostatectomy, with the Decipher high risk group being significantly enriched for metastatic events.[3] Dalela et al. developed and validated a nomogram which utilizes Decipher in conjunction with clinical and pathological variables to identify the subset of patients who are most at risk for metastatic recurrence.[4] A Decipher GC>0.6 was the most important variable in the model and these men had the best outcomes with early salvage radiotherapy.[4] This was recently validated by Lee et al. from analysis of a prospective outcomes registry.[12] Marascio et al. as well as Shahait et al., found, through analysis of two prospective outcomes registries, that only the Decipher high risk group had substantial benefit from the addition of early postoperative radiation while men with lower Decipher scores had few events and favorable outcomes overall with or without salvage therapy.[5,6]

Requests 4 & 5: 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.

For example, the guidelines for favorable intermediate risk (PROS-5) which allow for EBRT or brachytherapy alone, while those for unfavorable intermediate risk (PROS-6) which recommend addition of 4-6 months of ADT. These changes were adopted by NCCN based on the Zumsteg and Spratt et al., 2013 risk model that was developed and validated through retrospective analyses

(similar to those originally conducted for the Decipher genomic risk model) and is now considered as a standard of care for risk stratification by NCCN.[13]

Kim et al. and Herlemann et al. have found significant enrichment for postoperative adverse pathology among the men with high Decipher scores had worse pathologic outcomes.[8,10] For example, Herlemann found 41% of NCCN favorable intermediate with a GC>0.6 harbored adverse pathology (pT3b or lymph node invasion or high-grade disease) as compared to a 9% rate for those with a lower Decipher score.[10] Spratt et al., demonstrated that men with NCCN low or favorable intermediate risk results and a low Decipher risk score had excellent (100% freedom from distant metastasis at 10 years).[7]

Request 6: Three retrospective studies have demonstrated that Decipher can risk stratify NCCN high risk men. These studies demonstrate that a subset of NCCN high risk tumors have more favorable tumor biology (i.e., <10% risk of metastasis at 10 years), while the subset of tumors with higher genomic risk scores have >10% risk of metastasis at 10 years and should be considered for intensification of therapy.[14-16]

Request 7: Berlin et al. has shown, through analysis of a prospective registry, that among men with intermediate risk disease treated with EBRT alone (**without any hormone therapy)**, those with higher Decipher risk had a 50% 5-year probability of biochemical failure and a 15% probability of metastasis. Coversely, men with lower Decipher scores had a <5% biochemical failure rate (and no metastasis). The authors concluded that men harboring lower genomic risk tumors could be safely spared ADT, while those with higher genomic risk, who had substantial failure rates with EBRT monotherapy, may benefit from concurrent hormone therapy.[9]

Requests 9 & 10: SPARTAN, a phase III trial of patients with rapid PSA doubling time randomized to ADT alone vs. ADT + apalutamide demonstrated that patients with higher Decipher risk had poor outcomes on ADT alone and derived substantial benefit from the addition of apalutamide. Coversely, patients with lower Decipher risk had similar outcomes with ADT with or without apalutamide. These results show that men with a rapid PSA doubling time could be further risk stratified by Decipher testing of their primary tumors.[11,17]

Request 11: The NCCN panel for invasive breast cancer has included a table which ranks molecular assays for a given indication based on level of evidence. The NCCN panel for prostate cancer could help differentiate tumor-based testing based on evidence level supporting their clinical claims and intended use.

Request 12: Patients may experience pathological upgrade between time of biopsy and radical prostatectomy. If the index lesion was missed at initial biopsy, testing of the index lesion (i.e., the region of tumor with highest Gleason score and highest volume of disease) than additional testing of the presumptive index lesion from the radical prostatectomy sample may be warranted.

Summary

Since the publication of NCCN Prostate Cancer Guidelines, Version 2.2021, there have 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[7,8,10,14,15,18-30] or surgical specimens[2,4-6,16,22,31-46]. Decipher test results change practice management and the physician-patient shared decision for both urologists and radiation oncologists[5,6,32,47-54]. In addition, Decipher is highly correlated to other biomarkers of disease aggressiveness such as histologic grade and PI-RADS MRI score.[19,27-29,55] Aside from a myriad of retrospective studies of institutional cohorts and registries, Decipher has been validated in cohorts from Phase III trials such as RTOG 96-01[2] and SPARTAN[11,17] and is being prospectively tested in 7 NCI-funded Phase II and III trials. In summary, the Decipher assay is a highly validated prognostic biomarker as demonstrated in >40 studies of over 30,000 unique patients with long-term follow up and outcomes.[1-55]

Sincerely,

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