Submitted by: Mark D. Hiatt, MD, MBA, MS
Company: Guardant Health, Inc. *(505 Penobscot Drive, Redwood City, CA 94063)*
Contact: mhiatt@guardanthealth.com, 903-343-1188 *(mobile)*

Date of request: April 22, 2020

NCCN Guidelines Panel: Prostate Cancer, version 2.2020

FDA status: Guardant Health's **Guardant360** plasma-based comprehensive genomic profiling laboratory test has been designated for *Breakthrough Review* by the FDA (and is Clinical Laboratory Improvement Act-certified, College of American Pathologists-accredited, and New York Department of Health-approved).

On behalf of Guardant Health, I thank the Prostate Cancer Guidelines Panel and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection in cancer.

Request:

Please consider adding the suggestion that *a well validated plasma-based liquid biopsy may be used to support somatic tumor testing and MSI-H evaluation in advanced prostate cancer when tissue biopsy is infeasible* by including the following two additions:

Page PROSB-2 of 2

Current language	**Suggested language** (additions in ***blue***)
Somatic Tumor Testing . . . • Somatic testing may require repetition when prostate cancer progresses after treatment.	Somatic Tumor Testing . . . • Somatic testing may require repetition when prostate cancer progresses after treatment. • A well validated plasma-based NGS assay (liquid biopsy) may be used to evaluate somatic alterations (such as *BRCA1* and *BRCA2*) and MSI-H status in advanced prostate cancer when tissue biopsy is infeasible.
• DNA analysis for MSI and immunohistochemistry (IHC) for MMR are different assays measuring the same biological effect. If MSI is used, testing using an NGS assay validated for prostate cancer is preferred. Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing (NGS). J Immunother Cancer 2018;6:29.	• DNA analysis for MSI and immunohistochemistry (IHC) for MMR are different assays measuring the same biological effect. If MSI is used, testing using a tissue- or plasma-based NGS assay validated for prostate cancer is preferred. Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing (NGS). J Immunother Cancer 2018;6:29; Willis J, Lefterova MI, Artyomenko A, Kasi PM, Nakamura Y, Mody K, Catenacci DVT, et al. Validation of microsatellite instability detection using a comprehensive plasma-based genotyping panel. *Clin Canc Res* 2019;25:6909-15.

Rationale:

While tissue biopsy has been the historic standard for biomarker development and clinical trials, routine biopsy of prostate cancer metastases may be infeasible due to cost, morbidity, and low yield related to the bone-predominant metastasis from this type of cancer, occurring in 30% of patients within two years of castrate resistance and greater than 90% over the course of the disease.[1] A well validated plasma-based circulating tumor DNA (ctDNA) NGS assay may overcome the challenge of performing invasive repeat biopsies on bone metastases to interrogate somatic mutations and MSI-H status. (NGS is preferred over PCR because of the latter's inferiority.[2]) Peer-reviewed literature demonstrates high concordance between ctDNA and matched tissue NGS in prostate cancer for both somatic mutations and MSI-H.[3,4] ctDNA interrogation has also been shown to capture the evolution of the prostate cancer genomic landscape associated with subsequent therapies and disease progression, including resistance mechanisms to PARP inhibitors.[5,6]

Thank you for considering these clarifications.

Sincerely,

Mark D. Hiatt, MD, MBA, MS
Vice President, Medical Affairs | Guardant Health

[1] Den RB, George D, Pieczonka C, McNamara M. Ra-223 treatment for bone metastases in castrate-resistant prostate cancer: practical management issues for patient selection. *Am J Clin Oncol*. 2019;42(4):399-406..
[2] Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing (NGS). *J Immunother Cancer* 2018;6:29
[3] Wyatt AW, Annala M, Aggarwal R, Beja K, Feng F, Youngren J, Foye A, et al. Concordance of circulating tumor DNA and matched metastatic tissue biopsy in prostate cancer. *JNCI J Natl Cancer Inst 2017;*110(1):1-9.
[4] Willis J, Lefterova MI, Artyomenko A, Kasi PM, Nakamura Y, Mody K, Catenacci DVT, et al. Validation of microsatellite instability detection using a comprehensive plasma-based genotyping panel. *Clin Canc Res* 2019;25(23):6909-15.
[5] Hahn AW, Stenehjem D, Nussenzveig R, Carroll E, Bailey E, Batten J, Maughan BL, Agarwal N. Evolution of the genomic landscape of circulating tumor DNA (ctDNA) in metastatic prostate cancer over treatment and time. *Cancer Treatment and Research Communications* 2019;19.
[6] Goodall J, Mateo J, Yuan W, Mossop H, Porta N, Miranda S, Perez-Lopez R, et al. Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. *Cancer Discovery* 2017;7(9):1006-17.