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NCCN Guidelines Panel: Cervical Cancers

On behalf of Illumina, I respectfully request the NCCN Guideline Panel for Cervical Cancers to consider the requested updates pertaining to the evaluation of patients with cervical cancer.

Specific Changes (in red text)**:**
1. (CERV-12) Amend the footnote ff to Consider tumor mutational burden (TMB) testing as determined by a validated and/or FDA-approved comprehensive genomic profiling (CGP) assay.

2. (CERV-A 1 of 3) Amend the last bullet point to Consider TMB testing through a validated and/or FDA-approved comprehensive genomic profiling (CGP) assay.

3. (CERV-A 1 of 3) Add a new bullet point to the end under Pathologic assessment: Comprehensive genomic profiling with a validated and/or FDA-approved assay is informative for predicting rare pan-tumor targeted therapy opportunities.

4. (CERV-F 1 of 3) Amend footnote h to For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by a validated and/or FDA-approved comprehensive genomic profiling (CGP) test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Rationale:
Currently in the guideline there is no description of test type required to determine TMB status. The only technology capable of assessing TMB is next-generation sequencing (NGS). However, NGS assays can vary widely, by design, in the scope and variety of the gene mutations that can be assessed. Gene-panel size is a critical parameter in measuring TMB.[1] TMB can be calculated by whole exome sequencing (WES) or by large gene-panels called comprehensive genomic profiling (CGP) assays.

The most commonly used definition of CGP can be found on the Centers for Medicare & Medicaid Services (CMS) website.[2] It defined CGP as providing additional insight beyond individual gene hotspots provided by NGS-based Targeted Tumor Panels that identify somatic alterations known to occur in certain regions (i.e., "hotspot") within specific genes of interest. "[CGP] typically involves sequencing of entire exonic regions of genes of interest […], and may also include selected intronic regions". This definition states that CGP may also determine patterns of mutations seen across multiple genes, such as TMB.

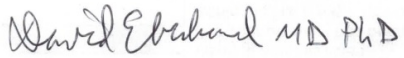
The distinction made between different types of NGS assays, and the types of biomarkers that they are suited to assess, is based on scientific evidence.[1,3] However, many oncologists in practice may not be familiar with the technical details of complex NGS assays and which types are appropriate for assessing TMB.[4] Consistent language describing NGS assays and capabilities such as TMB estimation with CGP may increase physician awareness of the differences between complex tests and improve access to appropriate testing and subsequent treatment with pembrolizumab for patients with unresectable or metastatic tumors who have progressed following prior treatment and who have no satisfactory

alternative treatment options.[5,6] Therefore, we ask that NCCN incorporate terminology that aligns more closely with the one presented by CMS.

The following articles are submitted in support of this proposed change.

1. Buchhalter, I. Size matters: Dissecting key parameters for panel-based tumor mutational burden analysis. *Int J Cancer*, 2019 Feb 15;144(4):848-858.
2. Medicare Coverage Database: Local Coverage Article, Billing and Coding: MolDX Targeted and Comprehensive Genomic Profile Next Generation Sequencing Testing in Cancer (A54901) https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=54901&ver=9&LCDId=36021&Date=&DocID=A56973&bc=gQAAAAIAIAAA&
3. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(1):34. Published 2017 Apr 19. doi:10.1186/s13073-017-0424-2
4. Merino DM, McShane LM, Fabrizio D, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer* 2020;8:e000147.
5. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study [published online ahead of print, 2020 Sep 10]. *Lancet Oncol*. 2020;S1470-2045(20)30445-9
6. KEYTRUDA (pembrolizumab) FDA approved label found at https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Thank you for your consideration,



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