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NCCN Guidelines Panel: Primary Cutaneous Lymphoma

On behalf of Adaptive Biotechnologies, we request that the NCCN Primary Cutaneous Lymphoma Guideline Panel review and consider the following modifications to the Guidelines.

Rationale

In 2018, the clonoSEQ® Assay was cleared by the FDA for the assessment of minimal residual disease (MRD) in the bone marrow of patients with multiple myeloma and acute lymphoblastic leukemia.[1,2] clonoSEQ is the first and only test approved for MRD assessment in these malignancies. The FDA has publicly recognized the rigor of clonoSEQ validation and has restated the need for a standardized MRD tool to aid in clinical management.[3] clonoSEQ is also available as a laboratory-developed test (LDT) for clonality assessment and disease monitoring in other B and T cell malignancies, such as CTCL, and other sample types, such as peripheral blood or skin.

In patients with cutaneous lymphomas, clonoSEQ is regularly used to assist with differential diagnosis by assessing the clonality of the diagnostic sample. Its use for clonality assessment has been shown to improve early detection of disease.[4-6] The Assay detects and evaluates TCR gene rearrangements with greater sensitivity and accuracy than other available testing modalities, which have significant false-negative rates.[4,5] In addition, clonoSEQ can be used to track the presence of malignant clones over time, which allows for the patient's response to be closely monitored and treatments to be tailored based on the clinical response.[5,7]

To ensure that all patient populations have access to this standardized and specific technology, Adaptive Biotechnologies has secured a positive coverage determination by Medicare and will continue to pursue private payer coverage policies (currently clonoSEQ has achieved > 200 million covered lives), thus removing a patient access barrier.[8]

Because of clonoSEQ's FDA authorization and the publication of new clinical data, we believe the NCCN committee might consider updating the Discussion section to include published data that demonstrate use of clonoSEQ in patients with Primary Cutaneous Lymphomas. Recent data from de Masson et al has shown the utility of using clonoSEQ to identify early-stage mycosis fungoides patients who are more likely to progress to aggressive disease via clonality assessment.[9]

In many cases, patients with mycosis fungoides (MF) present with stage 1 A/B disease. These patients usually have slow growing, or indolent, disease. However, a small subset of these patients will progress. Identifying which patients will progress is an urgent unmet medical need. When assessing the tumor clone frequency (TCF) by NGS, de Masson et al. were able to identify patients with a higher risk of progression in early stage (I A/B) MF. Of the 177 MF patients, those with a TCF >25% has a higher risk of progression ($P<0.001$) and decreased overall survival ($P<0.001$) compared to patients with a TCF of <25%. Therefore, TCR may be used to predict disease progression in early-stage MF. Identifying early-stage patients with a higher risk of progression may enable more tailored and efficacious clinical management.[9]

We would also like to acknowledge the committee for including a comprehensive review of NGS for assessing gene rearrangements within the current guidelines and would like to make the following minor recommendations.

Requested Modifications (based off version 2.2020)

- Page 14 (MFSS-1): Update Diagnosis, Essential section to add reference to NGS for gene rearrangement assessment (suggested updates in *red*):

        - Molecular analysis to detect clonal T-cell antigen receptor (TCR) gene rearrangements or other assessment of clonality (*NGS,* karyotype, array-CGH, or FISH analysis to detect somatic mutations or genetic alterations).

- Page 14 (MFSS-1): Update Diagnosis, Useful Under Certain Circumstances section to add a sub-bullet about utilizing NGS (in addition to flow cytometry) to assess peripheral blood for Sezary cells (suggested updates in *red*):
    - Assessment of peripheral blood for Sézary cells (in extensive skin disease where skin biopsy is not diagnostic in extensive patch or erythrodermic skin disease and/or strongly suggestive but not diagnostic of advanced-stage disease) including:
        - *NGS is useful to detect and quantitate an expanded T-cell population*

- Page 43 (LYMP-B): Consideration of language in 'Principles of Molecular Analysis in T-cell Lymphomas'
    - Bullet: 'Prognostic Value- Determination of clonal TCR gene rearrangement is an ancillary confirmatory test without prognostic value, except when used to assess relapsed or residual disease.'
    - The de Masson et al paper discussed above indicates that the detection of clonal TCR rearrangements at diagnosis was prognostic for determining which early-stage patients were more likely to progress to late-stage disease. Due to this evidence, we would ask the committee to consider modifying this statement.

- Discussion section, Version 2.2020: Update the discussion section to include information regarding the utility of NGS to:
    - Assist with differential diagnosis via clonality assessment[3-5]
    - Predict which early stage mycosis fungoides patient will progress[7]
    - Identify MRD in patients with Sezary Syndrome that were undetected by conventional flow cytometry[4]
    - Track and quantify response to treatment in CTCL patients.[4,6]

References

1. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2018. https://www.clonoseq.com/technical-summary
2. Ching T, et al. Analytical evaluation of the clonoSEQ Assay for establishing measurable (minimal) residual disease in acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma. *BMC Cancer*. In Press. 2020.
3. FDA authorizes first next generation sequencing-based test to detect very low levels of remaining cancer cells in patients with acute lymphoblastic leukemia or multiple myeloma [press release]. September 28, 2018. https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer
4. Kirsch I, et al. TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. Science Translational Medicine. 2015;7(308):308ra158.
5. Weng W, et al. Minimal Residual Disease Monitoring with High-Throughput Sequencing of T-cell Receptors in Cutaneous T Cell Lymphoma. Science Translational Medicine. 2013;5(214):214ra171.
6. Rea B, et al. Role of high-throughput sequencing in the diagnosis of cutaneous T-cell lymphoma. *Journal of Clinical Pathology*. 2018;71:814-820.
7. Rook AH, et al. Topical resiquimod can induce disease progression and enhance T-cell effector functions in cutaneous T-cell lymphoma. *Blood.* 2016;126(12):1452-61.
8. CMS. Local Coverage Article: MolDX: Clonoseq® Assay for Assessment of Minimal Residual Disease (MRD) in Patients with Specific Lymphoid Malignancies (A56270). https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56270&ver=5&Cntrctr=374&ContrVer=1&CntrctrSelected=374*1&DocType=Active&s=48&bc=AhAAAAIAgAAA&. Updated January 17, 2019. Accessed March 20, 2019.
9. de Masson A, et al. High-throughput sequencing of the T cell receptor B gene identifies aggressive early-stage mycosis fungoides. *Science Translational Medicine.* 2018;10(440). pii: eaar5894.