

Submitted by: Audrey Demaree, Senior Manager, Medical Affairs
Name: Lance Baldo, Chief Medical Officer
Company/Organization: Adaptive Biotechnologies Corporation
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (206) 279-2414
Email: lbaldo@adaptivebiotech.com
Date of request: Friday, May 22, 2020
NCCN Guidelines Panel: Acute Lymphoblastic Leukemia (Pediatric)



On behalf of Adaptive Biotechnologies, we request that the NCCN Pediatric Acute Lymphoblastic Leukemia 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 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.²

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, thus removing a patient access barrier.³

In addition to the specific requests below, we would like to request the consideration of additional data that demonstrates the utility of MRD assessment to the discussion section. Friend et al. retrospectively assessed the outcomes of pediatric ALL patients who either received or did not receive total-body irradiation (TBI) conditioning prior to transplant. It was found that patients that were MRD-negative prior to transplant, whether they received TBI or not, had lower relapse probability compared to MRD-positive patients (P=0.004). Importantly, it was shown that patients who were MRD-negative prior to transplant who did not receive TBI had similar outcomes to patients who were MRD-negative but did receive TBI (P=0.27). This is an important consideration, as TBI can cause many long-term side effect and brings to light the question of whether this population can be spared TBI based on MRD status.⁴

We would like to acknowledge the committee for including a comprehensive review of MRD testing methods, time points, and considerations within the current guidelines and would like to make the following minor recommendations.

Requested Modifications (based on Version 2.2020)

- Page 48 (ALL-F), Version 2.2020, Bullet 2: MRD is an essential component of patient evaluation over the course of sequential therapy. If **a validated MRD assessment technology with appropriate sensitivity is not available locally**, ~~patient is not treated in an academic center~~, there are commercially available tests. ~~available that should be used for MRD assessment.~~
- Page 48 (ALL-F), Version 2.2020: Update text to align with changes made to the 2019 Adult ALL Guidelines. Specifically, add the following statements (updates in **red**):
 - Add a note related to the sensitivity of PCR and NGS: 'Current 6-color flow cytometry can detect leukemic cells at a sensitivity of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs). **PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) bone MNCs.**
 - Add as a sub-bullet to the bullet titled 'Timing of MRD Assessment': **For some techniques, a baseline sample may be needed or helpful to facilitate future MRD assessments.**

- Discussion section, Version 2.2020: Update the discussion section to include recent data relating to the utility of NGS-MRD assessment in the pediatric setting.⁴

References

1. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2018.
<https://www.clonoseq.com/technical-summary>
2. 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/NewsEvents/Newsroom/PressAnnouncements/ucm622004.htm>
3. CMS. Local Coverage Article: MoIDX: 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 September 9, 2019.
4. Friend B, et al. The impact of total body irradiation-based regimens on outcomes in children and young adults with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation *Pediatric Blood & Cancer*. 2020;67(2):e28079.