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 Date of request: September 13, 2018
 NCCN Guidelines Panel: Acute Lymphoblastic Leukemia

On behalf of Adaptive Biotechnologies, we request that the NCCN ALL Guideline Panel review these suggested below modifications relevant to next-generation sequencing (clonoSEQ®).

Specific Changes:

1. On Page 10, Version 1.2018 (ALL-4): Add ‘Monitoring for MRD’ in Patients ≥65 years of age with substantial comorbidities who are in a CR. On page 12, Version 1.2018 (ALL-6): Add ‘Monitoring for MRD’ in Patients <65 years of age without substantial comorbidities who are in a CR.
2. Page 29, Version 1.2018: Add the following underlined text under ALL-F:
 - “Current 6-color flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs). clonoSEQ® can detect leukemic cells as a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) The concordance rate for detecting MRD between NGS, flow cytometry, and PCR is generally high. NGS has been shown to identify additional patients with MRD that were identified as MRD-negative by flow cytometry.”
3. The end of this request letter lists recent evidence in ALL related to clonoSEQ MRD assessment. We ask that you please consider adding this data into the ‘Discussion’ section under ‘Role of MRD Evaluation’.

FDA Clearance: The clonoSEQ Assay is currently under review by the FDA for use in monitoring acute lymphoblastic leukemia and multiple myeloma.

Rationale:

Request #1: ALL-F indicates that MRD assessment should be done ‘upon completion of initial induction’. The two populations (patients ≥65 years of age with substantial comorbidities who are in a CR and patients <65 years of age without substantial comorbidities who are in a CR) above do not note this MRD assessment on the pathway, so we are asking for its incorporation.

Request #2: This request is being made to provide fair and balanced information regarding other methodological approaches for MRD determination.

Numerous studies have assessed the correlation of MRD results by clonoSEQ and flow cytometry as well as comparative sensitivity. A summary of these studies is listed below.

Author	Concordant Results (+NGS/+flow or -NGS/-flow)	Discordant Results (NGS+/flow- or NGS-/flow+)	
Wood B, et al.	498 concordant MRD results (10^{-4})	10^{-4} : 55 samples NGS+/flow- 17 samples NGS-/flow+ *NGS-/flow- pts had superior survival compared to NGS+/flow- pts (P=0.036).	10^{-5} : 89 samples NGS+/flow- 6 samples
Sala Torra, et al.	51 concordant results	9 patients NGS+/flow- 1 patient NGS-/flow+	

Wu D, et al. 2014.	62 concordant MRD results	28 samples NGS+/flow- 0 samples NGS-/flow+
Pulsipher M, et al.	38 concordant MRD results	11 samples NGS+/flow- 3 samples NGS-/flow+
Wu D, et al. 2012.	21 concordant MRD results	10 samples NGS+/flow- 0 samples NGS-/flow+
Carlson CS, et al.	22 concordant MRD results	5 samples NGS+/flow- 0 samples NGS-/flow+
Faham M, et al.	95 concordant MRD results	10 samples NGS+/flow- 0 samples NGS-/flow+

Request # 3: Several recent studies have shown the ability of NGS-MRD to predict clinical outcomes. We ask that these studies be added to the discussion section of the Guidelines.

Wood et al. assessed end of induction (EOI) MRD in bone marrow samples in pediatric ALL patients. In the standard risk group (AALL0331), NGS MRD-negative patients had a 5-year EFS of 91% (P=0.0226) and 100% OS (P=0.126). At an MRD threshold of 10^{-4} , NGS and flow cytometry were able to predict event-free survival (P=0.009), however, NGS identified 55 additional patients with MRD that were MRD-negative by flow cytometry. These 55 patients had worse event-free survival than patients who were NGS MRD-positive and flow cytometry MRD-negative (P=0.036).

Pulsipher et al. assessed MRD pre- and post-transplant in patients. Pre-transplant, patients who were NGS MRD negative has significantly lower relapse rates and longer overall survival compared to patients who were MRD-positive (P<0.001; P=0.003). Post-transplant (day +30, day +100, 8 months post-transplant), patients who were NGS MRD negative had a significantly lower relapse and higher overall survival rates compared to NGS MRD positive patients (P<0.0001; P<0.001; P=0.0009).

Logan et al. determined that NGS-MRD positivity within 30 days pre-transplant and 100 days post-transplant was predictive of relapse (P=0.003; P<0.0001). Additionally, persistent NGS-MRD negativity (3 timepoints) was associated with better OS post-transplant versus patients with one positive MRD measurements (P<0.0001). The authors also assessed the ability for NGS MRD to identify disease prior to clinical relapse as assessed by morphology. In post-transplant blood samples, MRD-positive patients had a 100% positive predictive value for relapse. NGS was able to identify MRD-positivity 89 days before clinical relapse as assessed by morphology (P<0.0001).

Additionally, there have been numerous presentations and discussions lead by the FDA related to the use of MRD as a potential surrogate endpoint in ALL clinical trials. Recently, the FDA recognized MRD as a surrogate endpoint that was the basis for a drug approval in B-ALL.

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

1. Wood B, et al. *Blood*. 2018; 131(12):1350-1359.
2. Sala Torra, et al. *Biol Blood Marrow Transplant*. 2017;23(4):691-696.
3. Wu D, et al. *Clin Cancer Res*. 2014;20(17):4540-8.
4. Pulsipher M, et al. *Blood*. 2015;125(22):3501-8.
5. Wu D, et al. *Sci Transl Med*. 2012;4(134):134ra63.
6. Carlson CS, et al. *Nat Commun*. 2013;4:2680.
7. Faham M, et al. *Blood*. 2012;120(26):5173-80.
8. Logan AC, et al. *Biol Blood Marrow Transplant*. 2014;20(9):1307-13.
9. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. FDA 2018. Accessed: September 9, 2018.
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm>