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Positive Quality Intervention: clonoSEQ® Next Generation Sequencing for Minimum Residual Disease Testing in Chronic Lymphocytic Leukemia

Description: This document will outline the applicability, process, and importance of clonoSEQ® Assay using Next Generation Sequencing for minimal residual disease (MRD).

Background: The use of MRD status for clinical evaluation and recommendations regarding the assessment of disease burden during management of Chronic Lymphocytic Leukemia (CLL) was included in International Workshop on CLL and NCCN guidelines. Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after treatment is an important predictor of treatment efficacy and can assist with treatment decisions. clonoSEQ® is the first MRD test cleared by the FDA for multiple myeloma, CLL, and B-ALL. The clonoSEQ Assay is an in vitro diagnostic assay that utilizes NGS to identify the frequency and distribution of clonal sequences consistent with a malignant lymphocyte population in a sample. When the clonoSEQ Clonality ID assessment is conducted, the immune repertoire of the sample is checked for the presence of DNA sequences specific to "dominant" clone(s) consistent with the presence of a lymphoid malignancy. Each sequence that is being considered for MRD tracking is compared against a B cell repertoire database and assigned a uniqueness value that, together with its abundance relative to other sequences, is used to assign the sequence to a sensitivity bin which will be used in the estimation of the reported LoD and LoQ on the patient report.[1]

PQI Process:

- For fixed-duration targeted therapies:
  - Clonality ID test (using fresh or archival sample) at time of diagnosis to establish patient-specific sequences to track throughout the course of treatment
  - Combination therapy of CD20 monoclonal antibody with BCL-2 targeted therapies x 6 cycles
    - MRD tracking test (post cycle 6)
  - Single agent therapy x 6 cycles
    - MRD tracking test (post cycle 9 and post cycle 12)
  - Follow- up phase: Serial MRD monitoring (at least every 3 months post-treatment to determine disease kinetics; every 3-6 months thereafter for surveillance)
- For chemoimmunotherapy regimen:
  - Clonality ID test (using fresh or archival sample) at time of diagnosis to establish patient-specific sequences to track throughout the course of treatment
  - IGHV mutation analysis parallel with Clonality ID with the same sample
  - During treatment (MRD tracking test usually after 3 cycles of a 6 cycles regimen)
  - Post end of treatment (MRD tracking test usually after cycle 6)
  - Serial MRD monitoring on annual basis
- Sample order sets for EMR:
  - clonoSEQ Clonality ID, archived specimen
    - Specimen: Upon request within the clonoSEQ ordering portal, Adaptive can assist in retrieving an archived pathology specimen**;** this should be a high disease burden specimen representative of the patient's malignancy
    - Action: If utilizing the pathology retrieval service through Adaptive, place Clonality ID Test order in Adaptive portal, then fax clonoSEQ requisition form and a copy of the patient's diagnostic pathology report to Adaptive (866) 623-4408 or email the materials to clinicalservices@adaptivebiotech.com
  - clonoSEQ Clonality ID, fresh peripheral blood

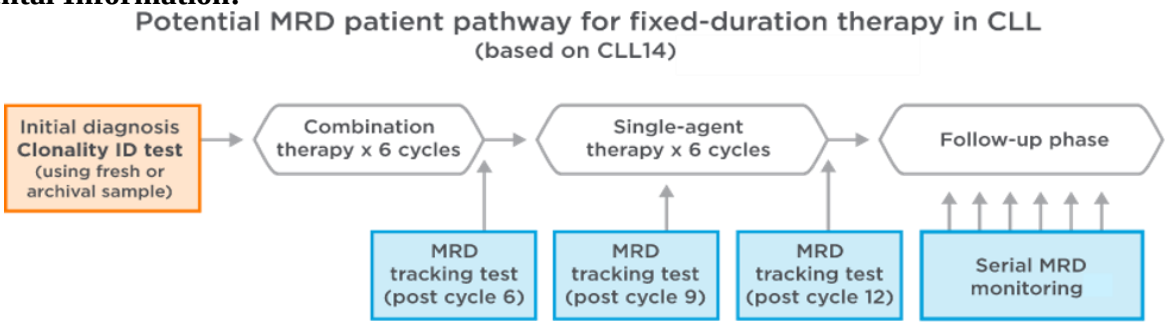
        - Specimen: fresh peripheral blood, 2 mL in an EDTA tube; this should be a high disease burden specimen representative of the patient's malignancy*
        - Action: Prepare 2 mL fresh peripheral blood in an EDTA tube
            - Patient navigators will place a Clonality ID order via the clonoSEQ diagnostic Portal and upload a copy of the requisition to the patient chart
            - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
    - clonoSEQ Clonality ID, fresh bone marrow aspirate
        - Specimen: fresh bone marrow aspirate, 1 mL in an EDTA tube; this should be a high disease burden specimen representative of the patient's malignancy*
        - Action: prepare 1 mL fresh bone marrow aspirate in an EDTA tube
            - Patient navigators will place a Clonality ID order via the clonoSEQ diagnostic Portal and upload a copy of the requisition to the patient chart
            - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
    - clonoSEQ MRD tracking, fresh bone marrow
        - Specimen: fresh bone marrow aspirate, 1 mL in an EDTA tube
        - Action: prepare 1 mL fresh bone marrow aspirate in an EDTA tube
            - Patient navigators will place an MRD Tracking order via the clonoSEQ Diagnostic portal and upload a copy of the requisition to the patient chart
            - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
    - clonoSEQ MRD tracking, fresh peripheral blood
        - Specimen: fresh peripheral blood, 2 mL in an EDTA tube*
        - Action: Prepare 2 mL fresh peripheral blood in an EDTA tube
            - Patient navigators will place an MRD tracking order via the clonoSEQ diagnostic portal and upload a copy of the requisition to the patient chart
            - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in adaptive kit for send out

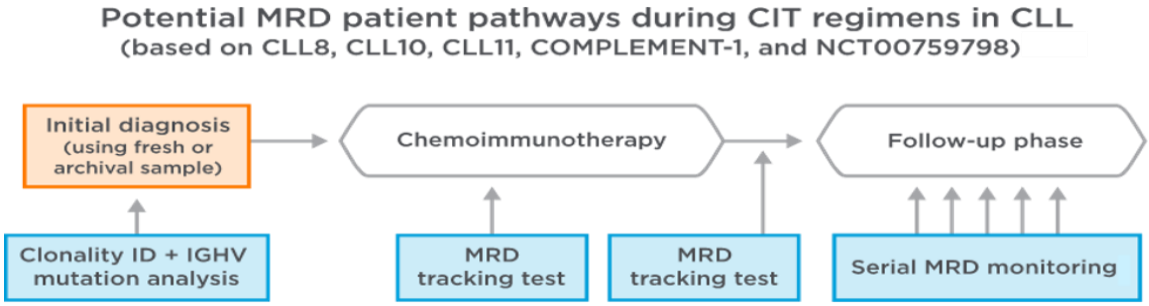
Patient-Centered Activities:

- Educate the patient on the importance of MRD testing:
    - MRD refers to the small number of cancer cells that can remain in the body during and after treatment and is one of the strongest predictors of outcomes in blood cancer
    - Consistent monitoring during and after fixed-duration therapy allows monitoring of peripheral blood as an alternative to frequent bone marrow assessments
    - ClonoSEQ is highly sensitive as it can detect one single cancer cell among a million healthy cells
- Communicate results, assessing treatment response and detecting changes in disease
- Ensure patient and physicians on understanding ongoing cancer journey and long-term outcomes
- Patient Assistance: NCODA Financial Assistance Tool

***** Regarding specimen handling process: ship overnight for next day 10:30 AM PT delivery; if same-day shipment is not an option, store specimen refrigerated; fresh specimens stored at ambient temperature should arrive at Adaptive within 4 days of collection, specimens stored refrigerated should arrive at Adaptive within 7 days of collection; ship frozen blood overnight on dry ice Mon-Thurs only, for next day 10:30 AM PT delivery.

Supplemental Information:





Serial MRD Monitoring

- Serial MRD monitoring refers to regular monitoring of disease burden via clonoSEQ testing as literature suggests that the kinetics of disease may be an important marker for prognosis (eg., sustained MRD negativity has been associated with improved outcomes) and clinical decision making (reducing or increasing therapy based on MRD results).
- "MRD Tracking" boxes for the CIT regimen pathways with each study (CLL8,10, 11) utilized different time frames as to when the tracking test was done. Therefore, it is up to clinical judgment of physicians.
- CAPTIVATE (Wierda et al), ADVANCE (Scarfo et al), and BOVEN (Soumerai et al) studies provide information of how to utilize MRD results to adapt therapy in CLL.

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