BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

Minimal Residual Disease (MRD) AHS-M2175

File Name:	minimal_residual_disease_mrd
Origination:	11/2020
Last CAP Review:	N/A
Next CAP Review:	11/2021
Last Review:	11/2020

Description of Procedure or Service

Minimal residual disease, also called measurable residual disease or MRD, refers to the subclinical levels of residual diseases, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and multiple myeloma (MM) (Horton & Steuber, 2020; Larson, 2020; Rajkumar, 2020; Stock & Estrov, 2020a, 2020b). MRD is a postdiagnosis, prognostic indicator that can be used for risk stratification and to guide therapeutic options when used alongside other clinical and molecular data (Schuurhuis et al., 2018). Many different techniques have been developed to detect residual disease; however, PCR-based techniques, multicolor flow cytometry, and deep sequencing-based MRD generally provide better sensitivity, specificity, reproducibility, and applicability than other techniques, such as fluorescence in situ hybridization (FISH), Southern blotting, or cell culture (Stock & Estrov, 2020b).

Related Policies:
Flow Cytometry AHS-F2019
Genetic Testing for Acute Myeloid Leukemia AHS-M2062
Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for minimal residual disease when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Minimal Residual Disease is covered

The use of minimal residual disease (MRD) testing is considered medically necessary for the following:

1. Minimal residual disease (MRD) testing by multiparameter flow cytometry and next-generation sequencing for individuals with multiple myeloma, including:

    a. During follow-up/surveillance after response to primary therapy

    b. After each treatment state (e.g. after induction, high-dose therapy/autologous stem-cell transplantation [ASCT], consolidation, and maintenance)

2. MRD testing by multiparameter flow cytometry (standardized ERIC method to at least a sensitivity of 10^{-4}) and next-generation sequencing for individuals with chronic lymphocytic leukemia or small lymphocytic lymphoma, including:

    a. After the end of treatment

    b. For consideration of therapy with lenalidomide for high-risk patients after first-line therapy

3. MRD testing of bone marrow aspirate samples by multiparameter flow cytometry and next-generation sequencing for individuals with acute myeloid leukemia, including:

    a. Upon completion of initial induction

    b. Before allogeneic transplantation

    c. Additional time points as guided by the regimen used

4. MRD testing of peripheral blood samples by PCR-based techniques for individuals with acute myeloid leukemia, including:

    a. Upon completion of initial induction

    b. Before allogeneic transplantation

    c. Additional time points as guided by the regimen used

    d. Serial monitoring in patients with molecular relapse or persistent low-level disease burden

5. MRD testing by multiparameter flow cytometry, PCR-based techniques, and next-generation sequencing for individuals with acute lymphoblastic leukemia, including:

    a. Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent MRD analysis

    b. Upon completion of initial induction

    c. Additional time points as guided by the regimen used

    d. Serial monitoring in patients with molecular relapse or persistent low-level disease burden

When Minimal Residual Disease is not covered

All other MRD testing by next-generation multiparameter flow cytometry, PCR, or next-generation sequencing is considered investigational.

Policy Guidelines

The ultimate goal of treating cancer has traditionally been "complete remission" (or response), which was defined as "absence of visible tumor" based on techniques, such as imaging and histological examination of tissue (Luskin, Murakami, Manalis, & Weinstock, 2018). However, cancer cells may remain undetected due to lack of sensitivity of conventional methods, leading to relapse. This subclinical amount of cancer cells is referred to as "minimal residual disease" or MRD (Bai, Orfao, & Chim, 2018). Many techniques have been developed to determine MRD, but multicolor flow cytometry and PCR-based, including next generation sequencing (NGS)-based, MRD techniques are the most commonly used (Rai & Stilgenbauer, 2020; Stock & Estrov, 2020b).

Multicolor flow cytometry (MFC), or multiparameter flow cytometry, can be used to determine MRD by measuring aberrant expression of antigens on cancer cells. MFC uses lasers of different colors to simultaneously determine specific immunophenotypic features of the cells within a sample. "Classic flow cytometry techniques using four to six colors have limited sensitivity and specificity for MRD detection. Current flow cytometry techniques use six to eight colors to assess MRD with a sensitivity which is approximately 10^{-4}, or about 0.5 to 1 log lower than that of polymerase chain reaction (PCR) (Stock & Estrov, 2020b)."

PCR-based MRD techniques, including NGS, amplify sequences of DNA unique to the cancerous cell. These techniques have amazing sensitivity; in fact, real-time quantitative PCR can be used to detect one cancerous cell from $10^4 – 10^5$ cells (Brüggemann et al., 2006; Stock & Estrov, 2020b). The targets of amplification can include T cell receptor (TCR) gene rearrangements, immunoglobulin heavy chain (IgH), or even fusion-gene transcripts (Del Giudice et al., 2019; Stock & Estrov, 2020b; van der Velden et al., 2003). Reverse transcriptase PCR-based MRD can also be used to detect cancer-related transcripts, such as *E2A/PBX1*, *TEL/AML1*, and *BCR/ABL* (Lee et al., 2003; Madzo et al., 2003; Stock & Estrov, 2020b).

ClonoSEQ (Adaptive Biotechnologies, Seattle, WA) is a commercially available NGS-based assay intended to assess MRD in certain types of cancer, such as multiple myeloma and acute lymphoblastic leukemia. The test identifies rearrangements in certain receptor gene sequences, which represent the level of MRD in a patient. This test traditionally uses genomic DNA extracted from bone marrow, but it may use circulating tumor DNA (ctDNA) (Adaptive_Biotechnologies, 2020a; Herrera et al., 2016). The report includes each nucleotide sequence identified for tracking residual disease, the amount of each identified marker (per million cells), and whether MRD is determined to be present in the sample (Adaptive_Biotechnologies, 2020b).

Analytical Validity

The EuroFlow Consortium has reported on the analytical validity of the use of an 8-color mFC for MRD. Theunissen et al. (2017) reported on the use of this methodology for B-cell precursor (BCP) acute lymphoblastic leukemia in a multi-center study on 319 patients. Using samples containing more than 4 million cells, they note concordant results in 93% of samples, and "[m]ost discordances were clarified upon high-throughput sequencing of antigen-receptor rearrangements and blind multicenter reanalysis of flow cytometric data, resulting in an unprecedented concordance of 98% (97% for samples with MRD < 0.01%). In conclusion, the fully standardized EuroFlow BCP-ALL MRD strategy is applicable in >98% of patients with sensitivities at least similar to RQ-PCR ($\leq 10^{-5}$), if sufficient cells ($>4 \times 10^6$, preferably more) are evaluated (Theunissen et al., 2017)." Another study reports the use of next-generation flow cytometry (NGF) using an "optimized 2-tube 8-color antibody panel" in five cycles to further increase the sensitivity. The authors report "a higher sensitivity for NGF-MRD vs conventional 8-color flow-MRD -MRD-positive rate of 47 vs 34% (P=0.003)-. Thus, 25% of patients classified as MRD-negative by conventional 8-color flow were MRD-positive by NGF, translating into a significantly longer progression-free survival for MRD-negative vs MRD-positive CR [complete response] patients by NGF (75% progression-free survival not reached vs 7 months; P=0.02)." Another study using a single-tube 10-fluorochrome analysis

NGF method of MRD in myeloma reports a five-fold increase in the target minimum of 5 X 10^6 white blood cells per acquisition (Royston et al., 2016).

The FDA included an assessment of the analytical validity of ClonoSEQ in their approval summary of a de novo request evaluation. 23 patients with multiple myeloma, 21 patients with acute lymphoblastic leukemia, and 22 patients with other lymphoid malignancies were included. The study tested three different volumes of DNA, 500ng, 2µg, and 20 µg. Six MRD levels were tested for each sample, which corresponded to the following amounts of malignant cells: 2.14, 6.13, 21.44, 61.26, 214.40, and 612.56. The authors found the coefficients of variance (%CV) to range from 72% at 2.14 cells to 21% at 612.56 cells. The authors noted that this precision trend was predictable as ClonoSEQ is dependent on the amount of cells evaluated instead of actual MRD frequency. Regarding DNA extraction reproducibility, all samples were found to pass the "pre-established acceptance criteria of ± 30% MRD frequency". Regarding precision of the nucleotide/base cells, the authors created a set of "baseline calibrating clonotype nucleotide sequences". From this set, replicates of each sample used to create the calibration sequence were created and the "disagreement rate" was identified. Out of 442.5 million nucleotides, ClonoSEQ was found to have a disagreement rate of 3.5 parts per million. The FDA notes a "Phred Score" of >30 is considered a "high-quality base call for NGS applications"; ClonoSEQ was scored at a 44.5. Regarding a comparison to multiparametic flow cytometry (mpFC), both ClonoSEQ and mpFC were tested at 5 dilutions (from $5x10^{-7}$ to $1x10^{-2}$), and both techniques were found to be of similar accuracy at frequencies above 1 x 10^{-4} (FDA, 2018a).

Clinical Validity and Utility

The FDA *de novo* approval document for ClonoSEQ contains three clinical validation studies. The first study for chronic lymphocytic leukemia (CLL) (CLL14-NCT02242942) included 336 patients to evaluate the ability of ClonoSEQ to predict progression-free survival (PFS). MRD positivity was defined as >1 x 10^{-5} [malignant cells]. The study found that patients found to be MRD-positive had an "event risk" of 9.45-times higher than the MRD-negative cohort. A 10-fold increase in MRD was also associated with a 2.35-fold increase in event risk. Patients under the 10^{-5} threshold (as determined by the ClonoSEQ assessment) were also found to have better PFS than patients above 10^{-5}, suggesting that clinical outcomes were better for the MRD-negative patients compared to MRD-positive ones (FDA, 2018a).

A second clinical validation study for multiple myeloma in ClonoSEQ's *de novo* approval document (DFCI 10-106) included 323 patients, and the authors intended "to assess the ability of clonoSEQ to predict progression-free survival (PFS) and disease-free survival (DFS)". ClonoSEQ was found to be predictive of PFS at the MRD threshold of 10^{-5} as well as over the entire cohort. Each 10-fold increase in MRD level was associated with a 70% increase in "event" rate across all MRD values (FDA, 2018a).

A third clinical validation study for acute lymphoblastic leukemia was described in the FDA's *de novo* approval document (AALL0232, AALL0331). 273 samples were included (210 MRD ≤10^{-4}, [negative], 63 MRD > 10^{-4} [positive]). The authors report that ClonoSEQ MRD-negativity status was found to predict event-free survival (EFS) at all ages. MRD-positivity status was also found to associate with a 2.74-fold higher event risk compared to MRD-negativity status. Across all MRD values, a 10-fold increase in ClonoSEQ MRD measurement was associated with a 50% increase in event rate, and MRD-negative patients were found to have longer event-free survival compared to patients with higher frequencies of malignancies (FDA, 2018a).

Hay et al. (2019) evaluated the impact of MRD negativity status on relapse rates of ALL (post-chimeric antigen receptor [CAR] T-cell therapy). 45 of 53 patients achieved an MRD-negative status per flow cytometry. At a median follow-up of 30.9 months, the authors found that event-free survival (EFS) and overall survival (OS) were "significantly" better in patients achieving MRD-negativity than patients that did not (median EFS: 7.6 months vs 0.8 months; median OS: 20 months vs 5

months). The authors also identified that the cytometric absence of the *IGH* index malignant clone was associated with better EFS (Hay et al., 2019).

Herrera et al. (2016) evaluated "whether the presence of ctDNA [circulating tumor DNA, measured with next-generation sequencing] was associated with outcome after allogeneic haematopoietic stem cell transplantation (HSCT) in lymphoma patients". 88 patients were included from a "phase 3 clinical trial of reduced-intensity conditioning HSCT in lymphoma". Patients with detectable ctDNA three months after HSCT were found to have inferior progression-free survival compared to patients without detectable ctDNA (58% vs 84%, 2-year PFS rate). Detectable ctDNA was found to confer a 10.8-times higher risk of relapse/progression and a 3.9-times higher risk of progression/death compared to the non-detectable ctDNA group. The authors concluded that "detectable ctDNA is associated with an increased risk of relapse/progression, but further validation studies are necessary to confirm these findings and determine the clinical utility of NGS-based minimal residual disease monitoring in lymphoma patients after HSCT" (Herrera et al., 2016).

Perrot et al. (2018) examined the prognostic value of MRD (measured with NGS) in multiple myeloma cases. 127 patients achieved MRD negativity (defined as "the absence of tumor plasma cell within 1 000 000 bone marrow cells ($<10^{-6}$)) at least once during maintenance therapy. At the start of therapy, MRD was found to be a "strong" prognostic factor for both progression-free survival and overall survival (hazard ratio = .22 and .24 respectively). The authors also identified 233 patients labeled as MRD-negative from a previous cohort, of which 120 were confirmed as MRD-negative with NGS (52%) (Perrot et al., 2018).

Friend et al. (2020) investigated the impact of NGS-MRD in predicting relapse in acute lymphoblastic leukemia (ALL) patients. The authors remarked that total body irradiation (TBI)-based regimens were the standard of care for ALL patients requiring allogeneic hematopoietic stem cell transplantation (HSCT), but this procedure has numerous harmful side effects; therefore, the authors hypothesized that identifying MRD-negative patients may avoid exposure to this radiation. The authors examined outcomes of 57 patients that received TBI and non-TBI regimens and found that relapse rates were similar for both methods of treatment. However, NGS-MRD positivity prior to treatment was "highly" predictive of relapse (for up to 3 years post-transplant). Based on their data, the authors suggested "that the decision to use either a TBI or non-TBI regimens in ALL should depend on NGS-MRD status, with conditioning regimens based on TBI reserved for patients that cannot achieve NGS-MRD negativity prior to allogeneic HSCT (Friend et al., 2020)."

Thörn et al. (2011) performed a comparative analysis of MFC and real-time quantitative polymerase chain reaction (RT-qPCR)-based MRD in pediatric acute lymphoblastic leukemia. The study, consisting of 726 follow-up samples from 228 children, using an MRD threshold of 0.1%, reports 84% concordance between the two different methods at day 29. For B-cell precursor ALL, the authors note that MFC was better at discriminating higher risk of bone marrow relapse (BMR) whereas RT-qPCR performed better for T-ALL. Regardless, the authors state, "MRD levels of ≥0.1%,detected by either method at day 29, could not predict isolated extramedullary relapse." They conclude that "both methods are valuable clinical tools for identifying childhood ALL cases with increased risk of BMR (Thörn et al., 2011)."

Wood et al. (2018) compared high-throughput sequencing (HTS) of *IGH* and *TRG* genes to flow cytometry (FC) to evaluate "measurable residual disease (MRD) detection at the end of induction chemotherapy in pediatric patients with newly diagnosed B-ALL [B-lymphoblastic leukemia]. 619 paired pretreatment and end-of-induction bone marrow samples were included. At an MRD threshold of 0.01%, both HTS and FC showed similar event-free survival (EFS) and overall survival (OS) for both MRD-positive and MRD-negative patients. However, HTS identified 55 more patients as "MRD-positive" compared to FC. These "discrepant" patients were found to have worse outcomes than FC MRD-negative patients. HTS was also found to identify 19.9% of "standard risk" (SR) without MRD at any detectable level with excellent EFS and OS (98.1% and 100% respectively). The authors suggested that "the higher analytic sensitivity and lower false-negative rate of HTS improves upon FC for MRD detection in pediatric B-ALL by identifying a novel subset

of patients at end of induction who are essentially cured using current chemotherapy and identifying MRD at 0.01% in up to one-third of patients who are missed at the same threshold by FC" (Wood et al., 2018).

Rawstron et al. (2016) conducted a parallel analysis of MRD using both ClonoSEQ and multiparameter flow cytometry in chronic lymphocytic leukemia as part of the European Research Initiative on CLL (ERIC) study. The MFC approach used within the ERIC study is validated to the level of 10^{-5}, and it consists of six different markers—CD5, CD19, CD20, CD43, CD49b, and CD81. The ERIC study reports that the ClonoSEQ method "provides good linearity to a detection limit of 1 in a million (10^{-6})". The authors also note, "A parallel analysis of high-throughput sequencing using the ClonoSEQ assay showed good concordance with flow cytometry results at the 0.010% (10^{-4}) level, the MRD threshold defined in the 2008 International Workshop on CLL guidelines… The combination of both technologies would permit a highly sensitive approach to MRD detection while providing a reproducible and broadly accessible method to quantify residual disease and optimize treatment in CLL (Rawstron et al., 2016)."

Thompson et al. (2019) evaluated 62 patients with chronic lymphocytic leukemia (CLL) that were considered negative for MRD by flow cytometry (sensitivity of 10^{-4}). Using ClonoSEQ, the authors found that 72.6% of these MRD-negative patients were MRD-positive by ClonoSEQ (a discordant result). Only 27.4% of patients were found to be negative by both methods. The authors also found that patients that were negative by both methods were found to have superior progression-free survival compared to patients that were only negative by flow cytometry, thereby suggesting that ClonoSEQ was a superior prognostic discriminator (Thompson et al., 2019).

Wang et al. (2019) published a study on the applicability of multiparameter (multicolor) flow cytometry (MFC) for detecting MRD to predict relapse in patients with AML after allogeneic transplantation. The researchers also compared MFC to MRD status determined using real-time quantitative polymerase chain reaction (RT-qPCR) from 158 bone marrow samples from 44 different individuals. "Strong concordance was found between MFC-based and RT-qPCR-based MRD status ($\kappa = 0.868$)." Moreover, for individuals in complete remission (CR), "the positive MRD status detected using MFC was correlated with a worse prognosis [HRs (*P* values) for relapse, event-free survival, and overall survival: 4.83 (<0.001), 2.23 (0.003), and 1.79 (0.049), respectively]; the prognosis was similar to patients with an active disease before HSCT [hematopoietic stem cell transplantation] (Wang et al., 2019)."

Carlson, Eckert, and Zimmerman (2019) published a cost-effectiveness study of NGS-based MRD testing during maintenance treatment for multiple myeloma. The authors compared use of MRD testing to no MRD testing. A Markov model with 6 health states was developed; "MRD positive or MRD negative, on or off treatment, relapsed, or dead." From there, the authors compared yearly NGS MRD to no MRD testing over a lifetime horizon. Overall, the authors found that "MRD testing saved $1,156,600 over patients remaining lifetime". Health outcomes were found to slightly favor MRD testing (0.01 quality-adjusted life years [QALYs]) compared to no testing. The authors concluded that "NGS MRD testing is cost saving, with potential QALY gains due to avoidance of [treatment-related adverse events] compared with no testing for MM patients on maintenance therapy (Carlson et al., 2019)."

Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN) (NCCN, 2019a, 2019b, 2019d, 2020a, 2020b)

The NCCN has published several relevant guidelines on management of minimal residual disease (MRD).

Multiple Myeloma (MM)

For MM, MRD is considered an "important" prognostic factor. The NCCN also recommends measuring MRD during follow-up/surveillance after response to primary therapy. Next-generation flow and next-generation sequencing (or both) are recommended for methodology, and a sensitivity of 1 in 10^5 (or better) is recommended for accuracy. MRD is a required criterion listed within the IMWG MRD response criteria. The NCCN notes that "for MRD there is no need for two consecutive assessments, but information on MRD after each treatment state is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance)." Sustained MRD-negative status is only confirmed when taken a minimum of 1 year apart, but "[s]ubsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)." The NCCN also notes that MRD information should be identified after each stage of treatment, but that testing should only be initiated "at the time of suspected complete response" (NCCN, 2020b). The NCCN also notes that MRD is being used in post-stem cell transplantation treatment assessments, too.

Lymphocytic Leukemia (Chronic and Small)

The NCCN remarks that "undetectable MRD in the peripheral blood at the end of treatment is an important predictor of treatment efficacy". The NCCN recommends performing MRD assessment at a sensitivity of 10^{-4} or better, and next-generation sequencing-based MRD assays have been shown to have sensitivity up to 10^{-6}. Within the chemoimmunotherapy maintenance therapy section, MRD is used when considering possible treatment with lenalidomide for high-risk patients (NCCN, 2019b).

Acute Myeloid Leukemia (AML)

The NCCN recommends measuring MRD "upon completion of initial induction" and "before allogenic transplantation". The NCCN also states, "Additional time points should be guided by the regimen used." However, NGS-based assays are still considered an "emerging" technology in AML (NCCN, 2019a).

Acute Lymphoblastic Leukemia (ALL)/Pediatric Acute Lymphoblastic Leukemia

The NCCN states that MRD is an "essential" component of patient evaluation over the course of sequential therapy, noting the prognostic significance of MRD. NGS is identified as one of the most frequently used methods for MRD assessment and is recognized as one of the most sensitive methods at detection levels of 10^{-6}. An entire section within the ALL guidelines is devoted to MRD assessment. They note the timing of MRD assessment to be as follows:

- "Upon completion of initial induction.
- Additional time points should be guided by the regimen used.
- Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
- For some techniques, a baseline sample may be needed or helpful for the MRD assessment to be valid (NCCN, 2020a)."

Overall, MRD is considered to have a high prognostic value and to have a role in identifying optimal treatments for patients, both adult and pediatric, with acute lymphoblastic leukemia (NCCN, 2019d, 2020a).

Hairy Cell Leukemia

The NCCN writes that "the clinical relevance of MRD [minimal residual disease] in patients with disease responding to therapy remains uncertain at this time" (NCCN, 2019c).

International Myeloma Working Group (IMWG, 2016) (Kumar et al., 2016)

The IMWG recommends assessing MRD response at a sensitivity of $1/10^5$ nucleated cells or better (Kumar et al., 2016).

European Myeloma Network (EMN) (Caers et al., 2018)

Regarding next-generation sequencing in assessment of MRD in Multiple Myeloma, the EMN writes that "Results from next-generation sequencing are highly concordant with flow-based MRD detection, highly reproducible and reach a sensitivity of 10^{-6}" and that the primary restraints for NGS are "a lack of standardization and limited commercial availability" (Caers et al., 2018).

American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) (2019) (Mikhael et al., 2019)

These joint guidelines focus on treatment of multiple myeloma. Their MRD-related recommendations are listed below:

- "There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including MRD status"
- "MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial"
- "There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD"
- "There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD)" (Mikhael et al., 2019).

European LeukemiaNet (ELN) MRD Working Party (Schuurhuis et al., 2018)

The ELN states, "Measurable residual disease (MRD; previously termed minimal residual disease) is an independent, postdiagnosis, prognostic indicator in acute myeloid leukemia (AML) that is important for risk stratification and treatment planning, in conjunction with other well-established clinical, cytogenetic, and molecular data assessed at diagnosis." The ELN remarks that quantitative PCR is applicable to approximately 40% of AML patients with "1 or more suitable abnormalities". However, NGS for MRD assessment may provide assessment to an additional 40%-50% of AML patients, as NGS can "theoretically, be applied to all leukemia-specific genetic aberrations". The ELN recommends a sensitivity of at least 1 / 103 cells, and states that NGS platforms will be used after careful validation (Schuurhuis et al., 2018).

International Workshop on Chronic Lymphocytic Leukemia (iwCLL) (Hallek et al., 2018)

The iwCLL published guidelines on CLL in 2018. In it, they consider MRD assessment to be a necessary component in identifying complete remission of CLL. The iwCLL also writes that eradication of leukemia is a "desired end point". They go on to state: "Use of sensitive multicolor flow cytometry, PCR, or next-generation sequencing can detect MRD in many patients who achieved a complete clinical response… Six-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of <1 CLL cell in 10 000 leukocytes (Hallek et al., 2018)."

College of American Pathologists (CAP) and the American Society of Hematology (ASH) (Arber et al., 2017)

This CAP/ASH joint guideline was published in 2017 and focuses on Initial Diagnostic Workup of Acute Leukemia (AL). The guideline strongly recommends that "For patients with suspected or confirmed AL, the pathologist or treating clinician should ensure that flow cytometry analysis or

molecular characterization is comprehensive enough to allow subsequent detection of MRD." The guideline also notes that MRD is a "powerful" predictor of adverse outcome in patients with AL (Arber et al., 2017).

European Society for Medical Oncology (ESMO) (Eichhorst et al., 2015; Heuser et al., 2020; Hoelzer et al., 2016; Moreau et al., 2017; Robak, Matutes, Catovsky, Zinzani, & Buske, 2015)

Chronic Lymphocytic Leukaemia

ESMO notes that "detection of MRD by four-colour flow cytometry has a strong prognostic impact. Patients who are MRD-negative after therapy show a longer response duration and survival (Eichhorst et al., 2015)."

Acute Lymphoblastic Leukaemia

ESMO writes that "Quantification of MRD is a major and well-established risk factor and should be obtained whenever possible for all patients also outside of clinical trials…If MRD is measured by flow cytometry, a good MRD response is often defined as less than 10^{-3} , although MRD levels less than 10^{-4} can be achieved with the 8–12 colour flow cytometers (Hoelzer et al., 2016)."

Multiple Myeloma

ESMO states, "There is a statistical relationship between the achievement of complete response (CR), MRD negativity and PFS [progression-free survival] or OS [overall survival] (Moreau et al., 2017)." They also include the 2016 response criteria of the IMWG MRD negativity criteria as part of the response evaluation.

Acute Myeloid Leukaemia

ESMO includes MRD status as part of the treatment algorithm for AML. They state, "Morphological enumeration of the blast percentage should be refined by immunophenotypic or molecular MRD assessment in patients with <10% blasts. ELN recommendations on MRD assessment in AML specify its clinical use and technical requirements. It is recommended to assess MRD by reverse transcriptase polymerase chain reaction (RT-PCR) for patients positive for *NPM1*^{mut}, *RUNX1-RUNX1T1, CBFB-MYH11* or *PML-RARA* fusion genes; ~40% of all AML patients. In the remaining patients, MRD should be assessed by MFC, which relies on antigens aberrantly expressed by leukaemic cells that can be found in >90% of AML patients. Many clinical studies have shown the strong prognostic impact of MRD, as measured by MFC, with levels 0.1% defined as positive (Heuser et al., 2020)."

Hairy Cell Leukaemia

Concerning hairy cell leukemia, ESMO notes, "Recently, monoclonal antibodies that detect the mutated BRAF protein have been developed and shown to be useful for the diagnosis and detection of minimal residual disease (MRD)." Within the section on response evaluation, ESMO states, "Immunophenotypic analysis of peripheral blood or bone marrow is not required but is useful to detect MRD… The eradication of MRD is generally not recommended in routine clinical practice. Assessment of response should be performed 4 – 6 months after treatment with 2-CldA and after 8 – 9 courses of DCF. Relapse is defined as any deterioration in blood counts related to the detection of hairy cells in peripheral blood and/or bone marrow (Robak et al., 2015)."

State and Federal Regulations

The FDA approved ClonoSEQ for marketing in 2018. The FDA notes that the test was approved through its "de novo premarket review pathway" and authorized Adaptive Biotechnologies to market this assay (FDA, 2018b). In its Decision Summary, the FDA states that the "The clonoSEQ Assay is an in vitro diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK, and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-Cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM). The clonoSEQ Assay measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment (FDA, 2018a).
A search of the FDA device database on 07/09/2020 of "minimal residual disease" and "MRD" resulted in no additional pertinent results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 88184, 88185, 81479, 0171U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Adaptive_Biotechnologies. (2020a). For Clinicians: ClonoSEQ Overview. Retrieved from https://www.clonoseq.com/for-clinicians/clonoseq-assay/

Adaptive_Biotechnologies. (2020b). For Clinicians: ClonoSEQ Reports. Retrieved from https://www.clonoseq.com/for-clinicians/clonoseq-report/

Arber, D. A., Borowitz, M. J., Cessna, M., Etzell, J., Foucar, K., Hasserjian, R. P., . . . Vardiman, J. W. (2017). Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med, 141*(10), 1342-1393. doi:10.5858/arpa.2016-0504-CP

Bai, Y., Orfao, A., & Chim, C. S. (2018). Molecular detection of minimal residual disease in multiple myeloma. *Br J Haematol, 181*(1), 11-26. doi:10.1111/bjh.15075

Brüggemann, M., Raff, T., Flohr, T., Gökbuget, N., Nakao, M., Droese, J., . . . Kneba, M. (2006). Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. *Blood, 107*(3), 1116-1123. doi:10.1182/blood-2005-07-2708

Caers, J., Garderet, L., Kortum, K. M., O'Dwyer, M. E., van de Donk, N., Binder, M., . . . Engelhardt, M. (2018). European Myeloma Network recommendations on tools for the diagnosis and monitoring of multiple myeloma: what to use and when. *Haematologica, 103*(11), 1772-1784. doi:10.3324/haematol.2018.189159

Carlson, J. J., Eckert, B., & Zimmerman, M. (2019). Cost-effectiveness of next-generation sequencing minimal residual disease testing during maintenance treatment for multiple myeloma. *Journal of Clinical Oncology, 37*(15_suppl), e19529-e19529. doi:10.1200/JCO.2019.37.15_suppl.e19529

Del Giudice, I., Raponi, S., Della Starza, I., De Propris, M. S., Cavalli, M., De Novi, L. A., . . . Foà, R. (2019). Minimal Residual Disease in Chronic Lymphocytic Leukemia: A New Goal? *Front Oncol, 9*, 689. doi:10.3389/fonc.2019.00689

Eichhorst, B., Robak, T., Montserrat, E., Ghia, P., Hillmen, P., Hallek, M., & Buske, C. (2015). Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 26 Suppl 5*, v78-84. doi:10.1093/annonc/mdv303

FDA. (2018a, 09/28/2020). EVALUATION OF AUTOMATIC CLASS II DESIGNATION FOR clonoSEQ® ASSAY DECISION SUMMARY. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170080.pdf

FDA. (2018b, 09/28/2018). 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. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer

Friend, B. D., Bailey-Olson, M., Melton, A., Shimano, K. A., Kharbanda, S., Higham, C., . . . Dvorak, C. C. (2020). 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. *Pediatr Blood Cancer, 67*(2), e28079. doi:10.1002/pbc.28079

Hallek, M., Cheson, B. D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Dohner, H., . . . Kipps, T. J. (2018). iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood, 131*(25), 2745-2760. doi:10.1182/blood-2017-09-806398

Hay, K. A., Gauthier, J., Hirayama, A. V., Voutsinas, J. M., Wu, Q., Li, D., . . . Turtle, C. J. (2019). Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. *Blood, 133*(15), 1652-1663. doi:10.1182/blood-2018-11-883710

Herrera, A. F., Kim, H. T., Kong, K. A., Faham, M., Sun, H., Sohani, A. R., . . . Armand, P. (2016). Next-generation sequencing-based detection of circulating tumour DNA After allogeneic stem cell transplantation for lymphoma. *Br J Haematol, 175*(5), 841-850. doi:10.1111/bjh.14311

Heuser, M., Ofran, Y., Boissel, N., Brunet Mauri, S., Craddock, C., Janssen, J., . . . Buske, C. (2020). Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. doi:10.1016/j.annonc.2020.02.018

Hoelzer, D., Bassan, R., Dombret, H., Fielding, A., Ribera, J. M., & Buske, C. (2016). Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 27*(suppl 5), v69-v82. doi:10.1093/annonc/mdw025

Horton, T. M., & Steuber, C. P. (2020, 01/17/2020). Risk group stratification and prognosis for acute lymphoblastic leukemia/lymphoblastic lymphoma in children and adolescents. *UpToDate*. Retrieved from https://www.uptodate.com/contents/risk-group-stratification-and-prognosis-for-acute-lymphoblastic-leukemia-lymphoblastic-lymphoma-in-children-and-adolescents

Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., . . . Avet-Loiseau, H. (2016). International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol, 17*(8), e328-e346. doi:10.1016/s1470-2045(16)30206-6

Larson, R. A. (2020, 04/17/2020). Remission criteria in acute myeloid leukemia and monitoring for residual disease. *UpToDate*. Retrieved from https://www.uptodate.com/contents/remission-criteria-in-acute-myeloid-leukemia-and-monitoring-for-residual-disease

Lee, S., Kim, D. W., Cho, B., Kim, Y. J., Kim, Y. L., Hwang, J. Y., . . . Kim, C. C. (2003). Risk factors for adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia in remission treated with allogeneic bone marrow transplantation: the potential of real-time quantitative reverse-transcription polymerase chain reaction. *Br J Haematol, 120*(1), 145-153. doi:10.1046/j.1365-2141.2003.03988.x

Luskin, M. R., Murakami, M. A., Manalis, S. R., & Weinstock, D. M. (2018). Targeting minimal residual disease: a path to cure? *Nat Rev Cancer, 18*(4), 255-263. doi:10.1038/nrc.2017.125

Madzo, J., Zuna, J., Muzíková, K., Kalinová, M., Krejcí, O., Hrusák, O., . . . Trka, J. (2003). Slower molecular response to treatment predicts poor outcome in patients with TEL/AML1 positive acute lymphoblastic leukemia: prospective real-time quantitative reverse transcriptase-polymerase chain reaction study. *Cancer, 97*(1), 105-113. doi:10.1002/cncr.11043

Mikhael, J., Ismaila, N., Cheung, M. C., Costello, C., Dhodapkar, M. V., Kumar, S., . . . Martin, T. (2019). Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. *Journal of Clinical Oncology, 37*(14), 1228-1263. doi:10.1200/JCO.18.02096

Moreau, P., San Miguel, J., Sonneveld, P., Mateos, M. V., Zamagni, E., Avet-Loiseau, H., . . . Buske, C. (2017). Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 28 Suppl 4*, iv52-iv61. doi:10.1093/annonc/mdx096

NCCN. (2019a, 12/23/2019). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Myeloid Leukemia Version 3.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

NCCN. (2019b, 12/20/2020). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Chronic Lymphocytic Leukemia / Small Lymphocytic Leukemia Version 4.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

NCCN. (2019c, 08/23/2019). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Hairy Cell Leukemia Version 1.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf

NCCN. (2019d, 11/25/2019). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Pediatric Acute Lymphoblastic Leukemia Version 2.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf

NCCN. (2020a, 01/15/2020). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Acute Lymphoblastic Leukemia Version 1.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

NCCN. (2020b, 05/08/2020). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Multiple Myeloma Version 4.2020. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Perrot, A., Lauwers-Cances, V., Corre, J., Robillard, N., Hulin, C., Chretien, M. L., . . . Munshi, N. (2018). Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood, 132*(23), 2456-2464. doi:10.1182/blood-2018-06-858613

Rai, K. R., & Stilgenbauer, S. (2020, 02/28/2020). Evaluating response to treatment of chronic lymphocytic leukemia. *UpToDate.* Retrieved from https://www.uptodate.com/contents/evaluating-response-to-treatment-of-chronic-lymphocytic-leukemia

Rajkumar, S. V. (2020, 03/03/2020). Multiple myeloma: Evaluating response to treatment. *UpToDate.* Retrieved from https://www.uptodate.com/contents/multiple-myeloma-evaluating-response-to-treatment

Rawstron, A. C., Fazi, C., Agathangelidis, A., Villamor, N., Letestu, R., Nomdedeu, J., . . . Ghia, P. (2016). A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. *Leukemia, 30*(4), 929-936. doi:10.1038/leu.2015.313

Robak, T., Matutes, E., Catovsky, D., Zinzani, P. L., & Buske, C. (2015). Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol, 26 Suppl 5*, v100-107. doi:10.1093/annonc/mdv200

Royston, D. J., Gao, Q., Nguyen, N., Maslak, P., Dogan, A., & Roshal, M. (2016). Single-Tube 10-Fluorochrome Analysis for Efficient Flow Cytometric Evaluation of Minimal Residual Disease in Plasma Cell Myeloma. *Am J Clin Pathol, 146*(1), 41-49. doi:10.1093/ajcp/aqw052

Schuurhuis, G. J., Heuser, M., Freeman, S., Bene, M. C., Buccisano, F., Cloos, J., . . . Ossenkoppele, G. J. (2018). Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood, 131*(12), 1275-1291. doi:10.1182/blood-2017-09-801498

Stock, W., & Estrov, Z. (2020a, 02/14/2020). Clinical use of measurable residual disease detection in acute lymphoblastic leukemia. *UpToDate.* Retrieved from https://www.uptodate.com/contents/clinical-use-of-measurable-residual-disease-detection-in-acute-lymphoblastic-leukemia

Stock, W., & Estrov, Z. (2020b, 04/21/2020). Detection of measurable residual disease in acute lymphoblastic leukemia. *UpToDate.* Retrieved from https://www.uptodate.com/contents/detection-of-measurable-residual-disease-in-acute-lymphoblastic-leukemia

Theunissen, P., Mejstrikova, E., Sedek, L., van der Sluijs-Gelling, A. J., Gaipa, G., Bartels, M., . . . van der Velden, V. H. (2017). Standardized flow cytometry for highly sensitive MRD measurements in B-cell acute lymphoblastic leukemia. *Blood, 129*(3), 347-357. doi:10.1182/blood-2016-07-726307

Thompson, P. A., Srivastava, J., Peterson, C., Strati, P., Jorgensen, J. L., Hether, T., . . . Wierda, W. G. (2019). Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. *Blood, 134*(22), 1951-1959. doi:10.1182/blood.2019001077

Thörn, I., Forestier, E., Botling, J., Thuresson, B., Wasslavik, C., Björklund, E., . . . Sundström, C. (2011). Minimal residual disease assessment in childhood acute lymphoblastic leukaemia: a Swedish multi-centre study comparing real-time polymerase chain reaction and multicolour flow cytometry. *Br J Haematol, 152*(6), 743-753. doi:10.1111/j.1365-2141.2010.08456.x

van der Velden, V. H. J., Hochhaus, A., Cazzaniga, G., Szczepanski, T., Gabert, J., & van Dongen, J. J. M. (2003). Detection of minimal residual disease in hematologic malignancies by real-time quantitative PCR: principles, approaches, and laboratory aspects. *Leukemia, 17*(6), 1013-1034. doi:10.1038/sj.leu.2402922

Wang, Z., Guo, M., Zhang, Y., Xu, S., Cheng, H., Wu, J., . . . Tang, G. (2019). The applicability of multiparameter flow cytometry for the detection of minimal residual disease using different-from-normal panels to predict relapse in patients with acute myeloid leukemia after allogeneic transplantation. *Int J Lab Hematol, 41*(5), 607-614. doi:10.1111/ijlh.13070

Wood, B., Wu, D., Crossley, B., Dai, Y., Williamson, D., Gawad, C., . . . Kirsch, I. (2018). Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. *Blood, 131*(12), 1350-1359. doi:10.1182/blood-2017-09-806521

Policy Implementation/Update Information

11/10/20 New policy developed. Reviewed by Avalon 3rd Quarter 2020 CAB. BCBSNC will provide coverage for minimal residual disease (MRD) when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 10/2020. **Notification given 11/10/2020 for effective date 1/1/2021**. (lpr)