

Minimal Residual Disease (MRD)

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I. Policy Description

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, 2022; Larson, 2020; Rajkumar, 2023; Stock & Estrov, 2022a, 2022b). 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 the best sensitivity, specificity, reproducibility, and applicability compared to other techniques such as fluorescence in situ hybridization (FISH), Southern blotting, or cell culture (Stock & Estrov, 2022b).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- 1) For individuals with multiple myeloma (MM), chronic lymphocytic leukemia (CLL), or small lymphocytic lymphoma (SLL), minimal residual disease (MRD) testing by multiparameter flow cytometry or next-generation sequencing (NGS) **MEETS COVERAGE CRITERIA**.
- 2) For individuals with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), MRD testing by multiparameter flow cytometry, PCR-based techniques, or NGS **MEETS COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 3) For all situations not addressed above (e.g., MRD testing in solid tumors), MRD testing by multiparameter flow cytometry, PCR, or NGS **DOES NOT MEET COVERAGE CRITERIA**.

III. Table of Terminology

Term	Definition
ABL	Abelson tyrosine kinase gene

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AL	Acute leukemia
ALL	Acute lymphoblastic leukemia
ALL	Pediatric acute lymphoblastic leukemia
AML	Acute myeloid leukemia
<i>AML1</i>	<i>Acute myeloid leukemia 1 protein gene</i>
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplantation
ASH	American Society of Hematology
B-ALL	B-cell acute lymphoblastic leukemia
<i>BCL1</i>	<i>B-cell lymphoma 1 gene</i>
<i>BCL2</i>	<i>B-cell lymphoma 2 gene</i>
BCP	B-cell precursor
BCR	Break point cluster gene
BM	Bone marrow
BMA	Bone marrow aspirate
BMR	Bone marrow relapse
BRAF	Proto-oncogene B-Raf/v-Raf murine sarcoma viral oncogene homolog B
CA	Cytogenetic abnormalities
CAP	College of American Pathologists
CAR	Post-chimeric antigen receptor
CBF	Core binding factor
<i>CBFB-MYH11</i>	<i>Cord binding factor subunit beta-myosin 11 fusion gene</i>
CCO	Cancer Care Ontario
CD19	Cluster of differentiation 19
CD20	Cluster of differentiation 20
CD43	Cluster of differentiation 43
CD49b	Cluster of differentiation 49b
CD5	Cluster of differentiation 5
CD81	Cluster of differentiation 81
2-CldA	Cladribine
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia
CMS	Centers for Medicare and Medicaid Services
CR	Complete response/complete remission
ctDNA	Circulating tumor deoxyribonucleic acid
CV	Coefficients of variance
DCF	Pentostatin
DFCI	Dana Farber Cancer Institute
DFS	Disease Free Survival
DJ	Diversity and joining segment rearrangement
DNA	Deoxyribonucleic acid
E2A	Transcription factor E2-alpha gene
EFS	Event free survival
ELN	European LeukemiaNet
EMN	European Myeloma Network
EOCT	End of combination therapy
ERIC	European Research Initiative on chronic lymphocytic leukemia
ESMO	European Society for Medical Oncology
EWS	Ewing sarcoma

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FC	Flow cytometry
FCR	Fludarabine cyclophosphamide and rituximab
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FUM3	Follow up month 3
gDNA	Genomic deoxyribonucleic acid
HR-NB	High-risk neuroblastoma
HSCT	Haematopoietic stem cell transplantation
HTS	High-throughput sequencing
IgH	Immunoglobulin heavy chain
<i>IGH</i>	<i>Immunoglobulin heavy chain gene</i>
IgK	Immunoglobulin K
IgL	Immunoglobulin L
IMWG	International Myeloma Working Group
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
J	Joining
<i>KIT</i>	<i>KIT proto-oncogene receptor tyrosine kinase</i>
LDTs	Laboratory developed tests
MFC/mFC	Multicolor flow cytometry
MFC	Mutliparameter flow cytometry
MM	Multiple myeloma
mpFC	Multi parametric flow cytometry
MRD	Minimal residual disease
MRD	Measurable residual disease
NCCN	National Comprehensive Cancer Network
NDMM	Newly diagnosed multiple myeloma
NGF	Next-generation flow cytometry
NGS	Next generation sequencing
NGS-MRD	Next-generation sequencing-minimal residual disease
non-TBI	Non-total body irradiation
NPV	Negative Predictive Value
<i>NPM1mut</i>	<i>Nucleophosmin 1 gene mutant allele</i>
OS	Overall survival
<i>PBX1</i>	<i>Pre-B-cell leukemia transcription factor 1 gene</i>
PCR	Polymerase chain reaction
PET-CT	Positron emission tomography -computed tomography
PFS	Progression-free survival
<i>PML-RARA</i>	<i>Promyelocytic leukemia-retinoic acid receptor alpha fusion gene</i>
PPV	Positive predictive value
QALYs	Quality adjusted life years
RQ-PCR/RT-qPCR	Real-time quantitative polymerase chain reaction
RRMM	Relapsed refractory multiple myeloma
RT-PCR	Reverse transcriptase polymerase chain reaction
<i>RUNX1-RUNX1T1</i>	<i>Runt-related transcription factor 1- RUNX1 partner transcriptional co-repressor 1 gene</i>
sCR	Stringent complete remission
SR	Standard risk
T-ALL	T-cell acute lymphocytic leukemia
TBI	Total body irradiation
TCR	T cell receptor

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TEL	<i>Translocation-Ets-leukemia virus gene</i>
TRG	<i>T cell receptor gamma locus gene</i>
uMRD	Undetectable minimal residual disease
VDJ	Variable-diversity-joining
VGPR	Very good partial response
WGS	Whole genome sequencing

IV. Scientific Background

The goal of treating cancer has traditionally been “complete remission” (or response), defined as “absence of visible tumor” based on techniques, such as imaging and histological examination of tissue (Luskin et al., 2018). However, some cancer cells may remain undetected due to a 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 et al., 2018). While many techniques have been developed to determine MRD, multicolor flow cytometry and PCR-based, including next generation sequencing (NGS), MRD techniques are the most commonly used (Rai & Stilgenbauer, 2023; Stock & Estrov, 2022b).

Multicolor flow cytometry (MFC), also known as multiparameter flow cytometry, can be used to identify MRD by measuring for the 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, 2022b).

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 a single cancerous cell from 10^4 – 10^5 cells (Brüggemann et al., 2006; Stock & Estrov, 2022b). The targets of amplification can include T cell receptor (TCR) gene rearrangements, the immunoglobulin heavy chain (IgH), or even fusion-gene transcripts (Del Giudice et al., 2019; Stock & Estrov, 2022b; van der Velden et al., 2003). Reverse transcriptase PCR-based MRD can also be used to detect cancer-related transcripts, including *E2A/PBX1*, *TEL/AML1*, and *BCR/ABL* (Lee et al., 2003; Madzo et al., 2003; Stock & Estrov, 2022b).

Proprietary Testing

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. This test identifies rearrangements in certain receptor gene sequences, representing the level of MRD in a patient. This test typically uses genomic DNA extracted from bone marrow but may use circulating tumor DNA (ctDNA) (Adaptive Biotechnologies, 2022a; Herrera et al., 2016). After testing, a report is provided which 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, 2022b).

Signatera™ is an MRD assay that uses ctDNA to attempt to inform the likelihood of cancer relapse earlier than standard of care tools. Whole exome sequencing of an individual's tumor tissue is first performed, allowing the identification of clonal somatic mutations which are expected to be present in all cells for the individual's specific tumor. The test is customized to an individual through selection of 16 clonal, single nucleotide variants (SNVs). After customization, a blood sample may be obtained from the individual, from which the 16 SNVs may be amplified and detected. An individual is considered MRD-positive when at least two SNVs from the set of 16 are detected (Natera, 2023).

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 (319 patients). Using samples containing more than four 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 over the target minimum of 5×10^6 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. A total of 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, corresponding 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 number of cells evaluated instead of the actual MRD frequency. Regarding DNA extraction reproducibility, all samples were found to pass the "pre-established acceptance criteria of $\pm 30\%$ MRD frequency." Regarding precision of the nucleotide/base calls, 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 had a Phred Score of 44.5. When compared to multiparametric flow cytometry (mpFC), both ClonoSEQ and mpFC were tested at five dilutions (from 5×10^{-7} to 1×10^{-2})s and both techniques were found to be of similar accuracy at frequencies above 1×10^{-4} (FDA, 2018).

In 2020, the FDA made a substantially equivalent decision on ClonoSEQ, providing in their summary an assessment with further analytical validity. Here, they looked at patients with CLL, measuring MRD levels from gDNA samples extracted from either bone marrow (22 patients) or blood samples (15 patients). The study tested six MRD levels in three different volumes of DNA: 500ng, 2µg, and 20 µg. In bone marrow samples, precision ranged from 59% CV at 2.14 cells to 20% CV at 612.56 cells. In blood samples, precision ranged from 53% CV at 3.10 cells to 19% CV at 765.70 cells. The authors note that “like BMA [bone marrow aspirate], the precision of the clonoSEQ assay in CLL blood is largely dependent on the number of malignant cells that are being evaluated by the assay.” From these data and those presented in the 2018 *de novo* approval document, the indications for use were developed. The authors report that “the clonoSEQ Assay measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological features” (FDA, 2020).

Othman Al-Sawaf et al. (2020) analyzed the clonal growth patterns of patients treated with venetoclax-obinutuzumab therapy within the CLL14 trial. In this case, MRD was analyzed using next-generation sequencing via the adaptive clonoSEQ assay with cutoffs of 10^{-4} , 10^{-5} , and 10^{-6} ; “the limit-of-quantification of the clonoSEQ assay is less than 10^{-6} .” 432 patients with untreated CLL were either treated with chlorambucil or venetoclax, in combination with obinutuzumab for the first six cycles. Using samples from peripheral blood (PB) collected every three to six months until nine years from last patient enrollment, the researchers found that two months post-treatment completion, among patients treated with venetoclax and obinutuzumab, 40% had uMRD levels $<10^{-6}$, 26% had uMRD levels that were $\geq 10^{-6}$ and $<10^{-5}$, 8% had uMRD levels $\geq 10^{-5}$ and $<10^{-4}$, 5% had uMRD levels $\geq 10^{-4}$ and $<10^{-2}$, and 3% had uMRD levels $\geq 10^{-2}$. In comparison, among patients treated with chlorambucil and obinutuzumab, 7% had uMRD levels $<10^{-6}$, 13% had uMRD levels $\geq 10^{-6}$ and $<10^{-5}$, 14% had uMRD levels $\geq 10^{-5}$ and $<10^{-4}$, 21% had uMRD levels $\geq 10^{-4}$ and $<10^{-2}$, and 26% had uMRD levels $\geq 10^{-2}$. Furthermore, “In a PFS landmark analysis after [end of treatment], patients in the [venetoclax-obinutuzumab] arm with MRD levels $\leq 10^{-5}$ had a 2-year PFS after [end of treatment] of approximately 93%, while patients with detectable MRD $>10^{-2}$ had a 2-year PFS of [approximately] 37%.” The average growth rate among patients treated with venetoclax-obinutuzumab was lower compared to the contrasting arm, and thus had a larger MRD doubling time. Because the clonal growth rate was lower, the study, using NGS, indicated “more effective MRD eradication and clonal growth modulation” (Othman Al-Sawaf et al., 2020; O. Al-Sawaf et al., 2020).

Clinical Utility and Validity

The FDA *de novo* approval document for ClonoSEQ contains two clinical validation studies. The first study for multiple myeloma in ClonoSEQ’s *de novo* approval document (DFCI 10-106) included 323 patients. The authors intended “to assess the ability of clonoSEQ to predict progression-free survival (PFS) and disease-free survival (DFS).” At the time of first MRD measurement, ClonoSEQ was found to be predictive of PFS at the MRD threshold of 10^{-5} . Each 10-fold increase in MRD level was associated with a 70% increase in “event” rate across all MRD values (FDA, 2018).

A second clinical validation study described in the FDA's *de novo* approval document was for acute lymphoblastic leukemia (AALL0232, AALL0331). A total of 273 samples were included (210 MRD $\leq 10^{-4}$, [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 associated 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 EFS compared to patients with higher frequencies of malignancies (FDA, 2018).

The FDA's 2020 substantially equivalent approval document for ClonoSEQ analyzed two separate studies to "support that MRD as estimated with the clonoSEQ Assay is prognostic of patient outcomes in CLL..." The first study was for chronic lymphocytic leukemia (CLL) (NCT02242942) and included 337 patients to evaluate the ability of ClonoSEQ to predict progression-free survival (PFS). Samples were collected three months or later following treatment (FUM3) and MRD positivity was defined as $> 1 \times 10^{-5}$ [malignant cells]. Patients found to be MRD-positive had an "event risk" 6.64 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. The authors also analyzed the results for other confounding factors and found "that the MRD level at FUM3 is a stronger predictor of PFS than age, sex, geographic region, Binet stage, or treatment arm of the clinical trial. Together, these results demonstrate the clinical validity of MRD measurement in CLL." This study also found that "patients with clonoSEQ MRD $\leq 10^{-6}$ or between 10^{-6} and 10^{-5} had longer PFS, followed by patients with MRD between 10^{-5} and 10^{-4} and patients with MRD $\geq 10^{-4}$ (log-rank $P = 4.902 \times 10^{-31}$, Figure 11). These data demonstrate that patients with MRD $\leq 10^{-5}$ have better outcomes than patients with MRD $> 10^{-5}$, and that increasing MRD levels above 10^{-5} are associated with an increased risk of progression within the follow-up time of this study" (FDA, 2020).

The second clinical validation described in FDA's 2020 substantially equivalent approval document was also for CLL (NCT00759798). This study was a "phase 2 clinical trial that evaluated six cycles of fludarabine, cyclophosphamide, and rituximab (FCR) in 111 front-line chronic lymphocytic leukemia (CLL) patients with clonoSEQ ID samples and a corresponding 137 clonoSEQ MRD samples also evaluated by 4-color flow cytometry at an MRD threshold of 10^{-4} (NCT00759798) and with pertinent co-variate data. Within this cohort of 111 patients with flow MRD results, bone marrow was available for 75 patients and blood was available for 62 patients, of which 26 patients provided both blood and bone marrow. Due to some missing clinical covariates, three patients that provided bone marrow only, were excluded from analyses requiring these covariates. There was an association between PFS and continuous clonoSEQ MRD measurement in both blood and bone marrow, after end of treatment, where PFS is defined as the time from start of treatment until death, disease progression, or last time of disease assessment ($p = 9.66 \times 10^{-4}$ for blood, $p = 2.13 \times 10^{-4}$ for bone marrow). Additionally, patients who were MRD negative at a threshold $\leq 10^{-5}$ had superior progression-free survival compared to patients with MRD $> 10^{-5}$ ($p = .02$ for blood and $p = 8.17 \times 10^{-5}$ for bone marrow... Taken together these results support the use of the clonoSEQ assay in CLL patients" (FDA, 2020).

Hay et al. (2019) evaluated the impact of MRD negativity status on relapse rates of ALL patients that post-chimeric antigen receptor [CAR] T-cell therapy. Per flow cytometry, 45 of 53 patients achieved an MRD-negative status. At a median follow-up of 30.9 months, the authors found that 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 five 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.” A total of 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 conferred 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 MM cases. A total of 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 as well as overall survival (hazard ratio = .22 and .24 respectively). From a previous cohort, the authors identified 233 patients labeled as MRD-negative, 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 ALL patients. Total body irradiation (TBI)-based regimens were the standard of care for ALL patients requiring allogeneic HSCT, but this procedure has numerous harmful side effects. The authors hypothesized that identifying MRD-negative patients may help some individuals 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 three 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 ALL. The study, consisting of 726 follow-up samples from 228 children, used an MRD threshold of 0.1% and reported at day 29 a 84% concordance between the two different methods. 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 $\geq 0.1\%$, 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-cell acute lymphoblastic leukemia]. A total of 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 CLL 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 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 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).

Z. 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 determined MFC and MRD status using real-time quantitative polymerase chain reaction (RT-qPCR) from 158 bone marrow samples from 44 different individuals and compared the statuses between the two. They noted that “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]” (Z. Wang et al., 2019).

Carlson et al. (2019) published a cost-effectiveness study of NGS-based MRD testing during maintenance treatment for MM. The authors compared use of MRD testing to no MRD testing. A Markov model with six 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).

Medina et al. (2020) evaluated MRD three months after transplantation in 106 myeloma patients, noting that “detecting persistent minimal residual disease (MRD) allows the identification of patients with an increased risk of relapse and death.” In this study, they compared the results of NGS with NGF, where they noted that “correlation between NGS and NGF was high ($R^2 = 0.905$). The 3-year progression-free survival (PFS) rates by NGS and NGF were longer for undetectable vs. positive patients (NGS: 88.7% vs. 56.6%; NGF: 91.4% vs. 50%; $p < 0.001$ for both comparisons), which resulted in a 3-year overall survival (OS) advantage (NGS: 96.2% vs. 77.3%; NGF: 96.6% vs. 74.9%, $p < 0.01$ for both comparisons). In the Cox regression model, NGS and NGF negativity had similar results but favoring the latter in PFS (HR: 0.20, 95% CI: 0.09-0.45, $p < 0.001$) and OS (HR: 0.21, 95% CI: 0.06-0.75, $p = 0.02$). All these results reinforce the role of MRD detection by different strategies in patient prognosis and highlight the use of MRD as an endpoint for multiple myeloma treatment” (Medina et al., 2020).

Goicoechea et al. (2021) examined MRD as a possible endpoint marker in MM. They note that while patients with MM that carry standard- or high-risk cytogenetic abnormalities (CA) are achieving similar CR rates, high-risk patients have an inferior PFS. They note that this “questions the legitimacy of CR as a treatment endpoint...” Using NGF cytometry to evaluate MRD in MM patients, they compared standard- vs high-risk CAs ($n=300$ and 90 , respectively) and identified mechanisms that determine MRD resistance in both patient subgroups ($n=40$). In patients achieving undetectable MRD with either standard- or high-risk CAs, the 36-month PFS rates were higher than 90%. In comparison, patients with persistent MRD had a median PFS of about three (standard-risk CA) and two (high-risk CA) years. They found that “further use of NGF to isolate MRD, followed by whole-exome sequencing of paired diagnostic and MRD tumor cells, revealed greater clonal selection in patients with standard-risk CAs, higher genomic instability with acquisition of new mutations in high-risk MM, and no unifying genetic event driving MRD resistance.” Ultimately, their results support “undetectable MRD as a treatment endpoint for patients with MM who have high-risk CAs and proposes characterizing MRD clones to understand and overcome MRD resistance” (Goicoechea et al., 2021).

Subhash et al. (2022) investigated the “feasibility of using whole-genome sequencing (WGS) data to design tumour-specific polymerase chain reaction (PCR)-based MRD tests (WGS-MRD)” for children with cancers with high risk of relapse, like ALL, high-risk neuroblastoma (HR-NB), and Ewing sarcoma (EWS). The significance of this study was that pediatric solid tumor MRD DNA-based assays currently remains experimental, and remains focused on mRNA, methylated DNA, or microRNA. Through their

experimentation, the researchers found that “sensitive WGS-MRD assays were generated for each patient and allowed quantification of 1 tumour cell per 10^{-4} (0.01%)- 10^{-5} (0.001%) mononuclear cells.” They also found that WGS-MRD and Ig/TCR-MRD assays were concordant in ALL, and the WGS-MRD assays “showed good concordance between quantitative PCR and droplet digital PCR formats.” The WGS-MRD assay clinical samples also correlated with disease course and was found to be more sensitive than RNA-based MRD assays. This demonstrated how WGS could aid the development of MRD assays for pediatric cancers as it has been done in adults (Subhash et al., 2022).

Kater et al. (2019) utilized the MURANO study to investigate the effects of a fixed duration treatment with venetoclax and rituximab on minimal residual disease. The study itself demonstrated “significant progression-free survival (PFS) benefit for fixed-duration venetoclax-rituximab compared with bendamustine-rituximab in relapsed/refractory chronic lymphocytic leukemia.” However, among patients who received venetoclax-rituximab, there was a “higher rate of PB [peripheral blood] undetectable MRD (uMRD; less than 10^{-4}) at EOCT [end of combination therapy] (62% v 13%) with superiority sustained through month 24 (end of therapy),” which predicted longer PFS. At the end of the therapy treatment period, 70% of patients remained in uMRD and 98% without disease progression. This demonstrated the correlation between uMRD and PFS using PB MRD in the setting of venetoclax-combination treatment (Kater et al., 2019).

Kim et al. (2022) investigated the clinical utility of NGF-based MRD assessment in a heterogeneous population of patients with multiple myeloma (MM) at the Samsung Medical Center in Korea and found that “sCR samples showed a lower MRD-positive rate (25%) than CR (43%) and VGPR (53%) samples, although the difference was not significant ($P=0.051$).” When evaluating survival analysis based on clinical response and MRD, “PFS in VGPR patients was lower than that in sCR/CR patients ($P<0.001$) ...whereas PFS in VGPR patients was lower than that in sCR/CR patients ($P<0.001$).” Cytogenetic risk survival analysis yielded similar results: “There was no significant difference in PFS between patients with high-risk and standard-risk cytogenetics ($P=0.222$)” and “Further analysis according to MRD status also revealed no significant difference in PFS in patients with standard-risk cytogenetics ($P=0.246$),” though it is worth noting that “among patients with high-risk cytogenetics, MRD-positive patients showed lower PFS than MRD-negative patients ($P=0.016$).” Overall, the authors concluded that “Sustained MRD negativity was only observed in patients with sustained sCR, and their PFS was superior to that of patients who were not MRD-negative ($P=0.035$),” though by their own admission the study was limited by the sample size ($n=12$ over 18 months) (Kim et al., 2022).

There is a growing pool of literature investigating the use of ctDNA-based MRD detection in the clinical context of solid tumors. Some studies suggest that inclusion of MRD assessment may offer some improvement over standard of care; this has been reported for gastrointestinal malignancies (Zhang et al., 2021), skin cancer (Eroglu et al., 2023; Khaddour et al., 2022), lung cancer (Zhong et al., 2023), and especially colorectal cancer, where several reports demonstrate potential benefits of ctDNA measurement, which include response monitoring, prognosis, post-surgical surveillance, chemotherapeutic management, and informing recurrence risk (Hofste et al., 2023; Sato et al., 2023; Tie et al., 2019; Tie et al., 2016; Y. Wang et al., 2019).

Signatera™ has been clinically validated across several cancer types for recurrence monitoring. In the context of colorectal cancer, Loupakis et al. (2021) demonstrated that a two-timepoint analysis of ctDNA (a baseline measure plus last follow-up time point—either the time of radiologic progression or last evidence of radiologic disease's absence) improved the sensitivity of the assay. For patients who were ctDNA positive at both timepoints, the authors reported that the assay demonstrated a sensitivity of 91.4%, specificity of 93.3%, and positive predictive value (PPV) of 96.7%. Reinert et al. (2019) also investigated the validity of ctDNA for MRD detection for individuals with stages I-III colorectal cancer and reported promising metrics; the test demonstrated a sensitivity of 88%, specificity of 98%, PPV of 93.3%, and negative predictive value (NPV) of 96.7%. However, Fakhri et al. (2022) recently determined that Signatera™ may not “provide advantages as a surveillance strategy compared with standard imaging combined with CEA levels when performed per National Comprehensive Cancer Network guidelines,” after a cohort study failed to demonstrate a sufficient ability (sensitivity) of the test to detect disease recurrence in individuals with resected colorectal cancer.

Coombes et al. (2019) described the ability of ctDNA to detect disease recurrence ahead of clinical or radiological approaches for individuals with breast cancer with a sensitivity of 89%, specificity of 100%, PPV of 100%, and NPV of 94%. Christensen et al. (2019) found that ctDNA accurately identified individuals diagnosed with advanced bladder cancer who eventually relapsed (sensitivity of 100% and specificity of 98%). For individuals with non-small cell lung cancer, Abbosh et al. (2017) reported that Signatera™ detected relapse with 93% sensitivity and 90% specificity.

While evidence supporting MRD analysis for solid tumors continues to emerge, a consensus on the clinical validity and utility of this approach has not yet been reached. Sullivan et al. (2023) cite several limitations of ctDNA-based approaches to the management of gastrointestinal cancer; O'Sullivan et al. (2023) argue that the utility of this technology in the context of non-small cell lung cancer is still investigational; Moding et al. (2021) cite a lack of prospective clinical trials confirming clinical utility of ctDNA MRD assessment in general; and, Jacome and Johnson (2023) argue that there is not yet consensus on how to apply the results of ctDNA-based testing in the management of colorectal cancer.

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

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

Multiple Myeloma (MM)

For MM, MRD is considered an “important” prognostic factor. The NCCN recommends measuring MRD during follow-up/surveillance after response to primary therapy “as indicated for prognostication.” Next-generation flow and next-generation sequencing (or both) are recommended for methodology and a sensitivity of 1 in 10⁵ (or better) is recommended for accuracy. The NCCN recommends to “consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS.” MRD is a required criterion listed within the IMWG MM 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). MRD tests should be initiated only at the time of suspected complete response.” Sustained MRD-negative status is only confirmed when taken a minimum of one 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 is being used in post-hematopoietic stem cell transplantation treatment assessments (NCCN, 2022).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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 with an assay at a sensitivity of 10^{-4} “according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.” NCCN also stated that “allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and six-color flow cytometry (MRD flow) are the two validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5} . Next-generation DNA sequencing (NGS)-based assays have been shown to be more sensitive, thus allowing for the detection of MRD at the level of 10^{-6} (NCCN, 2023c).

Acute Myeloid Leukemia (AML)

The NCCN recommends measuring MRD “upon completion of initial induction” and “before allogeneic HCT.” The NCCN also states, “Additional time points should be guided by the regimen used.” NGS-based assays to detect mutated genes are not routinely used in AML, as the sensitivity of PCR-based assays and flow cytometry is superior to what is achieved by NGS. The NCCN states that “if using flow cytometry to assess MRD, it is recommended that a specific MRD assay is utilized, but, most importantly, that it is interpreted by an experienced hematopathologist” since there are differences between “diagnostic threshold assessments and MRD assessments.” They also note that “some evidence suggest MRD testing may be more prognostic than *KIT* mutation status in CBF-AML, but this determination depends on the method used to assess MRD and the trend of detectable MRD” (NCCN, 2023b).

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 ALL therapy,” noting the prognostic significance of MRD. Three main techniques are used to assess for MRD: flow cytometry assays, real-time quantitative PCR assays, and NGS-based assays. NGS 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
- End of consolidation.
- 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 (i.e., prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.

The guidelines also recommend to “Consider retesting for MRD at first available opportunity” (NCCN, 2023a). Overall, MRD has a strong correlation with risks for relapse and is considered to have a high prognostic value. MRD has a role in identifying optimal treatments for patients, both adult and pediatric, with acute lymphoblastic leukemia (NCCN, 2023a, 2023e).

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, 2023d).

International Myeloma Working Group (IMWG, 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)

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)

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).

The ASCO also fully endorsed the “Initial Diagnostic Work-Up of Acute Leukemia” released jointly by the College of American Pathologists and the American Society of Hematology in 2018 (de Haas et al., 2018).

European LeukemiaNet (ELN) MRD Working Party

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 (Schoorhuis et al., 2018).

International Workshop on Chronic Lymphocytic Leukemia (iwCLL)

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)

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)

Chronic Lymphocytic Leukaemia

ESMO notes that “Detection of MRD by multicolour flow cytometry or RT-PCR has a strong prognostic impact following CIT73,74 as well as venetoclax plus CD20-antibody combinations. 75 Patients with undetectable MRD after therapy show a longer response duration and survival. Additional clinical consequences of MRD positivity after therapy with respect to treatment escalation remain unclear... Therefore, MRD assessment is not generally recommended for monitoring after therapy outside clinical studies. This may change soon, as increasing efforts are made to determine whether therapy with targeted agents could be discontinued on the basis of MRD status” (B. Eichhorst et al., 2021). The guidelines are also endorsed by the European Hematology Association (Barbara Eichhorst et al., 2021).

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, “One of the most significant improvements in the response criteria is the introduction of minimal residual disease (MRD) both in the bone marrow (BM) [using either next-generation sequencing or next-generation flow cytometry (NGF)] and outside the BM [using positron emission tomography-computed tomography (PET-CT); imaging MRD]. MRD negativity in the BM in patients who have achieved conventional complete response (CR) consistently correlates with prolonged progression-free survival (PFS) and overall survival (OS) in both newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM) patients.” ESMO also notes that “MRD has been found to be a

surrogate endpoint for PFS in patients receiving first-line treatment. Therefore, MRD may be used as an endpoint to accelerate drug development. The use of MRD to drive treatment decisions is under investigation” (Dimopoulos et al., 2021).

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-CIdA 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).

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

On August 5, 2020, the FDA approved ClonoSEQ, marketed by Adaptive Biotechnologies, as a substantially equivalent DNA-based test for minimal residual disease. It is “an in vitro diagnostic device that identifies and quantifies specific nucleic acid sequences isolated from human specimens to estimate the percentage of cells that harbor the specific sequence pathology test.” 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), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL). The clonoSEQ Assay measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological-p features” (FDA, 2020). 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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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IX. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period