Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions

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Instructions for Use

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Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kentucky	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Kentucky Only)
Louisiana	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Louisiana Only)
Nebraska	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Nebraska Only)
New Jersey	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Jersey Only)
North Carolina	None
Ohio	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Ohio Only)
Pennsylvania	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Pennsylvania Only)
Tennessee	Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for Tennessee Only)

Coverage Rationale

The use of multigene panels (50 genes or fewer) at initial diagnosis and/or recurrence or relapse is proven and medically necessary when ordered by a hematologist or oncologist for individuals with:

- Acute lymphoblastic leukemia; or
- Acute myeloid leukemia; or
- Multiple myeloma; or
- Myelodysplastic syndrome or myeloproliferative neoplasm is strongly suspected (as evidenced by order from hematologist/oncologist)

The use of Comprehensive Genomic Profiling (CGP) in an individual with relapsed/recurrent acute myeloid leukemia is proven and medically necessary (e.g., FoundationOne® Heme).

Clonality assessment with clonoSEQ® Clonality ID at initial diagnosis and Measurable Residual Disease (MRD) testing with clonoSEQ® MRD are proven and medically necessary when ordered by a hematologist or oncologist for individuals with:

- Acute lymphoblastic leukemia; or
- Multiple myeloma

Due to insufficient evidence of efficacy, all other molecular testing for hematologic cancer is unproven and not medically necessary. For companion diagnostic testing, refer to the Medical Policy titled Molecular Oncology Companion Diagnostic Testing.

Definitions

Comprehensive Genomic Profiling (CGP): A type of next-generation sequencing test that is able to detect all classes of genomic alterations, including cancer biomarkers, with a single sample (Singh et al., 2020).

Measurable Residual Disease (MRD): Also known as minimal residual disease, MRD is a term used to describe a very small number of cancer cells remaining in the body during and after cancer treatment. MRD measurement is most often used for blood cancers and can help providers form treatment plans and determine if treatment is working [National Cancer Institute (NCI) Dictionary of Cancer Terms, 2023a].

Next Generation Sequencing (NGS): New sequencing techniques that can quickly analyze multiple sections of DNA at the same time. Older forms of sequencing could only analyze one section of DNA at once (Kamps et al., 2017).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0017M	Oncology [diffuse large B-cell lymphoma (DLBCL)], mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements

CPT Code	Description
0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements, and minimal residual disease, reported as presence/absence
0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing of at least 20 molecular features (e.g., human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations
0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

Description of Services

Hematologic cancers begin in the tissues that form blood (e.g., bone marrow, cells of the immune system). Some examples of hematologic cancers include leukemia, lymphoma, and multiple myeloma (NCI, Dictionary of Cancer Terms, 2023b). Technologies used for molecular profiling of hematologic cancers vary, and include, but are not limited to, tests that evaluate variations in the genes, such as Next Generation Sequencing. The amount of genetic material evaluated can range from a single gene to the whole exome or genome. For the purposes of this policy, multi-gene analysis generally refers to a gene panel containing five or more genes, though some exceptions may apply as noted specifically in the policy. Results of molecular profiling may assist individuals and healthcare providers with determining prognosis and selection of more effective and targeted cancer therapies (Chantrill et al., 2015).

Multi-Gene Panel Use in Hematological Cancers

In a 2018 multicenter study including 2,035 individuals, Grinfeld et al. sequenced coding exons from 69 identified myeloid cancer genes in individuals diagnosed with myeloproliferative neoplasms. Using this information, a genomic classification was developed to predict outcomes for individuals. In all, 33 of the genes had driver mutations in at least 5 individuals, with JAK2, CALR or MPL as the only abnormality in 45% of participants. Volumes of driver mutations increased in parallel with age and advancement of disease. Demographic variables, germline polymorphisms and driver mutations independently predicted disease and eight genomic subgroups with distinct clinical phenotypes were defined. Ultimately, prognostic models which could generate tailored prediction of clinical outcomes in individuals with chronic-phase myeloproliferative neoplasms and myelofibrosis were created and predicted/observed outcomes correlated in internal cross-validation of a training group and an independent external group. The authors concluded that their characterization may enable personalized prediction of outcomes and support individuals diagnosed with myeloproliferative neoplasms.

Song et al. (2017) conducted a review of the literature comparing the clinical utility of a variety of genomic profiling techniques in the treatment of myelodysplasias (MDS). They noted that the common defects in MDS that should be identified are del5q, trisomy 8, del20q, del7q, monosomy 7 and complex karyotypes. Each aberration has different prognostic and management challenges, so accurate identification of genomic abnormalities is important for a clear diagnosis and to optimize treatment strategies. The authors compared findings from the literature for routine cytogenetics, FISH, spectral karyotyping (SKY), SNP array, CGH, and SNP+CGH for the ability to detect the common defects in MDS. The authors concluded that no single technology provides all the information necessary for the clinician to create informed treatment plans, and that a combination of techniques is required. The authors favored routine cytogenetics, FISH and SNP+CGH, but noted that additional efforts are needed to standardize testing and bioinformatics, and further technological advances are needed to overcome the limitations of diverse techniques.

Evans et al. (2016) studied the diagnostic utility of SNP+CGH array to identify unexplained cytopenia in 83 MDS patients and compared results with 18 normal bone marrow controls. Array analysis was done in parallel with standard cytogenetics, FISH, flow cytometry, and morphology. Forty-five percent of patients were diagnosed with MDS, 33% were normal, and 8% had other pathological disorders. 57% of the MDS patients had normal cytogenetics, but the SNP+CGH array found significant cryptic chromosome aberrations. In MDS patients with abnormal cytogenetics, the array essentially matched the chromosome results and did not add any new information. Overall, the SNP+CGH array analysis contributed significantly to the diagnostic yield in indeterminate morphology cytopenic patients.

Weinhold et al. (2016) reported clinical outcomes of GEP testing in relation to treatment type for subgroups of patients (n = 1,217) with multiple myeloma (MM) who participated in the University of Arkansas for Medical Sciences Total Therapy (TT) trials. Using log-rank tests for GEP data, the researchers identified 70 genes linked to early disease-related death. The UAMS GEP70 risk score is based on the ratio of the mean expression level of up-regulated to down-regulated genes among the 70 genes. Most up-regulated genes are located on chromosome 1q, and many down-regulated genes map to chromosome 1p. The predictor enabled the reliable identification of patients with shorter durations of complete remission, event-free survival, and overall survival that constitute 10-15% of newly diagnosed MM patients. The authors' reported that impact of treatment differs between molecular subtypes of MM and that GEP gives important information that can help in clinical decision-making and treatment selection. Future studies should address whether strategies maximizing exposure to proteasome-inhibitors can further improve outcome in the MS subgroup. The authors' note that comparison of GEP data of multiple paired samples showed differences in risk signatures, indicating the co-existence of HiR and LoR subclones (manuscript in preparation). Possibly, cells of a LoR subclone were collected at relapse in these patients. the addition of thalidomide significantly improved outcome of LoR cases from maintenance and that outcome of LoR was improved further by the addition of bortezomib. The authors comment that they could not detect a significant improvement for HiR cases, but this may be due to a lack of statistical power.

Peterson et al. (2015) conducted a study to determine the clinical utility and diagnostic yield, plus examine the rationale, of including microarray analysis in the diagnosis of hematological neoplasias. Twenty-seven patients with hematological malignancies were evaluated by chromosome analysis, FISH and CGH or CGH+SNP arrays. Nearly 90% of chromosome abnormalities found in the patients were also identified by microarray. Of 183 CNVs found, 52% were additional anomalies that were not found by routine cytogenetics or FISH. 65% were < 10 Mb in size. Balanced rearrangements were not found by

microarray, but of 19 rearrangements that appeared “balanced” by routine cytogenetics, 7 had alterations found by microarray at the breakpoints. The authors concluded that CGH provided clinicians with advantages in identification of cryptic imbalances and clonal abnormalities in non-dividing cells with poor chromosome morphology and therefore had potential to be integrated as a patient management tool.

Laurie et al. (2014) compared the SNP array results of 278 symptomatic CLL patients with > 50,000 subjects from the GENEVA consortium of genome wide association studies, which analyzed people with a range of medical conditions and healthy controls. The CLL patients were also analyzed by FISH to determine performance and concordance between the SNP array and FISH. When a parameter of 20% abnormal cells was used as a cutoff, the concordance rate between the SNP array and FISH was 98.9%. The array found 8.4% of cases with UPD which cannot be detected by FISH. In 214 CLL patients with SNP results, 1,112 genetic anomalies were found, of which 628 were considered acquired. This was a higher percentage and anomalies were unique in the CLL group when compared to the GENEVA cohort and suggests that late stage CLL has recurrent acquired anomalies that do not occur in precursor conditions or in the general population. The clinical significance of this finding is not clear, however, SNP based array was demonstrated to be a valid analysis tool.

Kolquist et al. (2011) examined the clinical utility of CGH in myelodysplasias. They noted that only half of myelodysplasias (MDS) patients show genomic abnormalities using routine cytogenetics, yet this group of patients is characterized by ineffective hematopoiesis, cytopenia, and a 30% risk of developing acute myeloid leukemia (AML). They hypothesized that using CGH to test patients who were cytogenetically normal would reveal cryptic genomic alternations that would improve prognosis, managing disease progression, and determining the suitability and efficacy of molecularly targeted therapy. They analyzed 35 samples by CGH derived from patients with a diagnosis and suspicion of MDS who also had known abnormal karyotypes. 80% of samples had new chromosomal aberrations that had not been revealed by cytogenetics or FISH. An additional 132 cryptic abnormalities were found including deletions of known oncogenes, such as NF1, RUNX1, RASSF1, CCND1, TET2, DNMT3A, HRAS, PDGFRA and FIP1L1. Overall, the authors concluded that CGH in combination with routine cytogenetics provided additional clinically relevant information that could better direct the care of the patients analyzed.

Detection of Measurable Residual Disease (MRD) in Hematologic Cancers

Hayes performed a Molecular Test Assessment on the FDA-approved clonoSEQ® test for measurement of MRD when used to monitor changes in disease burden during and after treatment of B-cell acute lymphoblastic leukemia (B-ALL) and multiple myeloma (MM) using bone marrow (BM) samples and in patients with chronic lymphocytic leukemia (CLL) using BM or peripheral blood (PB) samples. Although the overall body of evidence is low in quality, data from 2 studies addressing clinical validity suggest that clonoSEQ has a lower sensitivity threshold for MRD detection than other types of MRD detection tests [allele-specific oligonucleotide- polymerase chain reaction (PCR) and flow cytometry] in individuals with CLL or MM. At this time, no peer-reviewed evidence was identified that reported improved clinical outcomes resulting from clonoSEQ testing [Hayes, clonoSEQ (Adaptive Biotechnologies), 2022, updated 2023].

Pulsipher et al. (2022) sought to define biomarkers predictive of relapse by evaluating MRD detection and B-cell aplasia in individuals with acute lymphoblastic leukemia (ALL) who had undergone treatment with (immunocellular) tisagenlecleucel therapy. A total of 143 individuals who participated in the ENSIGN and ELIANA studies provided samples. Of these, 426 samples [301 bone marrow (BM) and 125 blood] from 109 participants passed quality control and were included in the evaluation. The researchers found that detection of MRD > 0 via next generation sequencing (NGS) in BM was significantly associated with relapse. If B-cell recovery occurred within the first year of treatment, hazard ratio (HR) for relapse was 4.5 [95% confidence interval (CI), 2.03–9.97; P < 0.001]. Measured at day 28, multivariate analysis was found to have independent association of BM NGS-MRD > 0 (HR = 4.87; 95% CI, 2.18–10.8; P < 0.001) and B-cell recovery (HR = 3.33; 95% CI, 1.44–7.69; P = 0.005) with relapse. At 3 months from treatment, BM NGS-MRD HR increased to 12 (95% CI, 2.87–50; P < 0.001), but B-cell recovery was not independently predictive (HR = 1.27; 95% CI, 0.33–4.79; P = 0.7). The authors concluded that BM NGS-MRD can consistently predict risk, allowing acceptable time for consideration of potential therapy for relapse prevention (e.g., hematopoietic cell transplantation or CAR-T cell infusion).

Using data from four phase three studies (POLLUX, CASTOR, ALCYONE, and MAIA), Cava et al. (2022) investigated MRD measurement in relapsed/refractory multiple myeloma (RRMM) and transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM). Each of these studies had already found that daratumumab-based treatment improved MRD negativity and lowered the risk of progression or death by roughly half when compared to standard-of-care treatment. In this study, the researchers performed a pooled analysis for associations between individuals who attained complete response or better with MRD-negative results and progression-free survival (PFS). NGS was used for MRD assessment. Sensitivity threshold was 10^{-5}.

Results from all four studies were pooled at the participant level, as was data for individuals with TIE NDMM and patients with RRMM who received ≤ 2 prior lines of therapy (≤ 2 PL), and PFS was assessed by both response and MRD status. The researchers found that individuals with complete response or better and MRD negativity had improved PFS compared to those who did not achieve complete response or were MRD positive [TIE NDMM and RRMM hazard ratio (HR) 0.20, P < .0001; TIE NDMM and RRMM ≤ 2 PL HR 0.20, P < .0001], regardless of therapy used or disease setting. Complete response or better with MRD negativity was associated with improved PFS based on a time-varying Cox proportional hazard model. Ultimately, the authors concluded that their findings, based on a large-scale analysis and high-quality methodology, support complete response or better with negative MRD results as a factor in prognostication for PFS in RRMM and TIE NDMM. This is in alignment with findings from other studies which indicate that negative MRD results are related to improved long-term outcomes and that negative MRD findings are important in the prediction of outcomes when compared to other prognostic indicators for MM.

In a systematic review and meta-analysis Short et al. (2022) assessed MRD impact on clinical outcomes in AML. Studies reporting association between MRD and overall survival (OS) or disease-free survival (DFS) in AML were included in the review (n = 48). In studies including only individuals in complete remission, estimated 5 year OS for MRD-negative group was 67% [95% Bayesian credible interval (CrI), 53-77%] and for MRD-positive group was 31% (95% CrI, 18-44%). Greater DFS and OS was associated with MRD-negative results regardless of analytic sensitivity or MRD threshold used. Of those in complete remission, studies using MRD cutoff of less than 0.1% showed the greatest benefit related to MRD negativity. Beneficial impact associated with MRD negativity was seen regardless of timing of assessment or type of assay performed. Noted is the lack of survival reporting for individuals with lesser responses or according to specific MRD level in most of the studies analyzed, so no estimate of impact can be made in those situations. In addition, current MRD assay for AML can only achieve a sensitivity of 1×10^{-4} to 1×10^{-5}. As such, absence of detectable MRD does not rule out residual disease that may eventually lead to relapse. In this systematic review, using a threshold of 0.1%, 5 year DFT of 63% indicates that a significant portion of MRD-negative individuals will still relapse. In opposition, a small percentage (16%) of individuals who were MRD-positive were still disease free at 5 years. Overall, the authors concluded that for individuals with AML in remission, MRD-negativity correlates with higher DFS and OS, which provides further support for the use of MRD in individuals with AML.

A 2021 NICE innovation briefing states that the clonoSEQ test for MRD shows improved standardization, sensitivity and specificity when compared with other techniques for MRD assessment. However, there is a lack of randomized studies in the evidence at this time.

Wierda et al. (2021) published an expert review and consensus recommendations addressing the use of measurable residual disease (MRD), also referred to as minimal residual disease, to evaluate disease burden during and after treatment of chronic lymphocytic leukemia (CLL). They note that undetectable MRD status at the end of treatment has been associated with prognostic significance in CLL, corresponding with favorable, progression-free and overall survival rates with use of chemoimmunotherapy. Because of this, assessment of MRD is being studied in CLL clinical trials, and the need for further standards for terminology and clinical outcomes reporting is recognized. This consensus represents the outcome of a 174-member panel of international and interdisciplinary experts who collaborated to pinpoint key questions on the issues surrounding MRD in CLL and provide recommendations for further study. The authors provide recommendations for standardized nomenclature, methodology, assay requirements, tissue to be used, timing/frequency of MRD assessment (at least 2 months after completion of last treatment and in alignment with response assessment), and the significance of undetectable MRD (U-MRD). The authors state that current guidelines do not recommend routine MRD testing in practice for CLL at this time; this is the subject of study in clinical trials.

In a 2020 publication, Martinez-Lopez et al. provided the results of a retrospective single-institution study evaluating MRD in 234 individuals with MM, including 159 participants with NDMM and 75 participants with RRMM. Each individual underwent NGS of immunoglobulin genes for MRD assessment at a sensitivity threshold of $10^{-}6$. Overall, individuals with MRD negativity at $10^{-}6$ and $10^{-}5$ had better median PFS. Of the individuals with NDMM, the median PFS was enhanced for those with MRD negativity at $10^{-}5$ compared to those with MRD negativity at $< 10^{-}5$ (PFS: 87 months vs 32 months; P < .001). Likewise, in the RRMM group, median PFS was improved for those with MRD negativity at $10^{-}5$ over those with MRD negativity at $< 10^{-}5$ (PFS: 42 months vs 17 months; P < .01). Based on these results, the researchers assert that MRD is a valuable marker for prognosis in NDMM as well as RRMM and advocate for prospective study to further confirm this.

In a 2019 expert consensus, Short et al. provided recommendations for assessment of MRD in adults with ALL, affirming that MRD which has persisted after initial therapy is a compelling predictor of survival and relapse in individuals with ALL, but

nothing the controversial nature surrounding the best use of this information to inform clinical decision-making. The document addresses MRD assessment methods as well as the prognostic/predictive impact of MRD in ALL, directing that in adults undergoing frontline treatment, bone marrow should be used to assess MRD as per the following timeframe: after the end of induction, in early consolidation (approximately 3 months after start of therapy) and then approximately every 3 months for at least 3 years. In individuals with relapsed or refractory ALL undergoing salvage therapy, MRD should be evaluated, at a minimum, at the time of morphological remission and at the end of treatment. The document further outlines recommended therapeutic approaches based on MRD results. The authors not that NGS holds substantial promise in refining risk assessment and improving clinical decision-making in ALL, but large prospective studies to further evaluate this technology and the utility of peripheral blood MRD assessment are needed.

A systematic review and meta-analysis exploring the impact of MRD-negativity on the improvement of PFS or overall survival (OS) in individuals with CLL after upfront chemotherapy or chemo-immunotherapy was published by Molica et al. in 2019. A total of 11 studies were included overall; nine provided information on PFS, and six provided information on OS. Substantial differences between the different studies were found for PFS and OS, based on tests of heterogeneity. Superior PFS was associated with undetectable MRD in the overall population (P < .001). Undetectable MRD was also a predictor of longer OS overall (P < .001). In individuals who achieved complete remission, undetectable MRD was associated with better PFS (P = .01), but not OS (P = .82). The researchers indicate that their results further bolster the evidence supporting the use of MRD assessment as an outcome in clinical trials focused on CLL.

Thompson et al. (2019) used NGS with a sensitivity of $10^{-}6$ to assess MRD in 62 individuals with CLL who had been found to have bone marrow undetectable MRD per multicolor flow cytometry with sensitivity of $10^{-}4$ at the end of treatment with first-line fludarabine, cyclophosphamide, and rituximab (FCR). Because individuals with CLL sometimes relapse despite reaching an undetectable MRD (especially if unmutated *IGHV* is present) when an assay with sensitivity of $10^{-}4$ has been used, the researchers speculated that a more sensitive MRD evaluation may be warranted. MRD assessment with NGS was performed on samples including bone marrow, peripheral blood, and plasma. Of the 62 individuals who underwent MRD reassessment with NGS, only 27% had undetectable MRD based on the NGS-based assessment. Individuals who had mutated *IGHV* had greater likelihood of having undetectable MRD by NGS after treatment (EOT; 41% vs 13%, P = .02) than those without mutated *IGHV*. The median follow up time was 91.6 months. The authors concluded that greater sensitivity of MRD testing ($10^{-}6$ vs $10^{-}4$) results in additional prognostic information for individuals with CLL. They caution, however, that factors associated with relapse are complex and likely include elements beyond the absolute level of MRD detection. Additional study is recommended.

The efficacy of targeted NGS to identify MRD in patients with acute myeloid leukemia (AML) was studied by Jongen-Lavrencic et al. (2018). Between 2001 and 2013, a total of 482 patients ranging in age from 18-65 with newly diagnosed AML were included. NGS of 54 genes that are often present in AML patients was performed at diagnosis and after induction therapy during complete remission. The end points analyzed were 4-year relapse, relapse free survival and overall survival. Results were compared with flow cytometry (FC). The authors discovered an average of 2.9 mutations per patient, of which at least one single mutation could serve as an indicator of residual disease, in 430 patients. These patients then had NGS testing repeated on bone marrow after induction therapy, and they were in complete remission. Persistent mutations were found in 52% and were highly variable across the genes analyzed. DTA mutations were most common, persisting at rates of 79%, whereas *RAS* pathway mutations cleared, persisting at an average rate of about 9%. The authors noted that DTA mutations are common gene mutations in individuals with age related clonal hematopoiesis, and likely represent non-leukemic clones rather than persistent malignant disease. After DTA mutations were excluded, the detection of MRD was associated with a significantly higher relapse rate than no detection (55% vs. 32%), lower relapse-free survival (37% vs. 58%) and overall survival (42% vs. 66%). The results of NGS were compared to FC in a subset of 340 patients. Concordant results for detection or non-detection of MRD were found in 69% of patients. The four-year relapse rate was 73% among patients in whom both assays were positive, 52% among those who had residual disease on sequencing but not on flow cytometry, 49% among those who had residual disease on flow cytometry but not on sequencing, and 27% among those in whom both assays were negative. Multivariate analysis found that combining the two assays gave a high prognostic value to the rate of relapse (P <.001), relapse free survival (P < .001) and overall survival (P = .003).The authors concluded that persistent mutations associated with clonal hematopoiesis did not have prognostic value, whereas the detection of MRD during complete remission using NGS with FC had significant additive prognostic value.

The Food and Drug Administration (FDA) reviewed information submitted by Adaptive Technologies on their clonoSEQ assay, which included data from currently ongoing studies (FDA, 2018). They noted that clinical validity was demonstrated in a retrospective analysis of 273 patients with ALL, on ongoing study of 323 patients with multiple myeloma, and separate study of 706 patients with multiple myeloma. Patients who had a negative MRD results had a longer event free survival. In 2020,

clonoSEQ was cleared by the FDA for MRD detection and monitoring of individuals with CLL as well (FDA, 2023). This clearance was the result of data from two clinical trials: the CLL14 study (NCT02242942), which included 337 individuals, demonstrated that participants with an undetectable MRD (blood) per the clonoSEQ test had an almost 7-fold reduction in risk of progression of their disease when compared with those who were found to be MRD positive. In addition, 30 months after treatment, the probability of disease progression for individuals who could be evaluated was only 5% in those that has an undetectable MRD, versus 36% I individuals that had detectable disease. The second study (Thompson et al., 2019, discussed above) also found clonoSEQ MRD test results to be predictive of outcomes when both blood and bone marrow samples were used.

An important prognostic factor in B-lymphoblastic leukemia (B-ALL) is early response to combination induction chemotherapy. End of induction response is typically measured by multiparametric flow cytometry (FC) or allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The analytical sensitivity for FC is 0.01%, and ASO-PCR is .001%, but requires the development of patient specific probes. Wood et al. (2018) reviewed the clinical validity of a new technical approach of using high throughput sequencing (HTS) of IGH and TRG genes to FC for determining minimal residual disease (MRD). The study used 619 paired pretreatment and end-of-induction bone marrow samples from Children's Oncology Group studies AALL0331 and AALL0232 (clinicaltrials.gov). The samples were evaluated by HTS and FC for event free survival and overall survival. Using an MRD threshold of 0.01%, HTS and FC show similar 5-year event free survival and overall survival rates. There was high discordance between HTS and FC in number of patients identified; HTS identified 55 more patients (39%), and these patients had worse outcomes than FC MRD negative patients. HTS also identified 19% of standard risk patients without MRD at any detectable level, which was correlated with excellent outcomes. Overall HTS had a high sensitivity and lower false-negative rate than FC in this analysis.

Avet-Loiseau et al. (2015) reported on the use of FC and NGS in the Intergroup Francophone du Myélome/ Dana-Farber Cancer Institute (IFM/DFCI) 2009 trial to measure MRD in the IFM arm of the study. This trial enrolled 700 patients under 66 years of age and randomized them to either receive either 8 cycles of VRD (Velcade-Revlimid-Dexamethasone) (arm A), or 3 VRD cycles, high-dose melphalan, followed by two consolidation VRD cycles (arm B). All patients received a lenalidomide maintenance for 12 months. A total of 246 patients were evaluated by NGS using the LymphoSight platform, and before maintenance, 87 patients were negative, 80 were low-positive, and 79 were positive. After maintenance, 178 were tested, and 86 patients were negative, 52 were low-positive, and 40 were positive. Using a cutoff of 10^{-6}, patients below this threshold had a pre-maintenance progression free survival (PFS) of 86%, vs. 53% for patient > 10^{-6}. In the post-maintenance group, these numbers were 90% and 59% respectively. When compared with results from seven color FC, of 72 patients who were positive with FC, 67 were also positive with NGS. In the FC negative group, of the 163 patients, 51 were positive by NGS. In this subgroup, the 3-year PFS was 86% for the NGS negative patients compared to 66% for the NGS negative patients in the pre-maintenance group. In the post-maintenance group, the numbers were 91% and 65% respectively. The authors concluded that NGS was able to predict PFS in this study.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCR)

In a joint clinical practice guideline, ASCO and CCR (Mikhael et al., 2019) provided recommendations on treatment of multiple myeloma. Recommendations include:

- There is currently insufficient evidence to make modifications to maintenance therapy based on depth of response, including MRD status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate)
- The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. 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 (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate)
- It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak)
- Depth of response for all patients should be assessed by International Myeloma Working Group (IMWG) criteria regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate)

- 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 (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate)
- In the case of relapse, repeat risk assessment should be performed at time of relapse, including bone marrow with FISH for myeloma abnormalities seen with progression, including 17p and 1q abnormalities (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong)

College of American Pathologists (CAP) and American Society of Hematology (ASH)

CAP and ASH convened a panel of experts to review the literature and establish a guideline for appropriate lab testing for the initial diagnosis of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and ambiguous acute leukemias (ALs). The guideline was endorsed by ASCO. The experts reviewed the literature and using an evidence-based methodology intended to meet recommendations from the Institute of Medicine, a set of guidelines was developed. The guidelines were reviewed by an independent panel and were made available for public comment. The outcome was 27 guidelines addressing clinical information required by the pathologist and recommended laboratory testing. Chromosome microarray is broadly addressed as one potential test in several statements that refer to "molecular genetic testing," which may also include FISH, RT-PCR, or DNA methylation studies. These include:

- "In addition to morphologic assessment (blood and BM), the pathologist or treating clinician should obtain sufficient samples and perform conventional cytogenetic analysis (i.e., karyotype), appropriate molecular-genetic and/or FISH testing, and FCI. The flow cytometry panel should be sufficient to distinguish acute myeloid leukemia (including acute promyelocytic leukemia), T-ALL (including early T-cell precursor leukemias), B-cell precursor ALL (B-ALL), and AL of ambiguous lineage for all patients diagnosed with AL. Molecular genetic and/or FISH testing does not, however, replace conventional cytogenetic analysis." (Statement 5. Strong Recommendation)
- "For patients who present with extramedullary disease without BM or blood involvement, the pathologist should evaluate a tissue biopsy and process it for morphologic, immunophenotypic, cytogenetic, and molecular genetic studies, as recommended for the BM." (Statement 11. Strong Recommendation)
- "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." (Statement 12. Strong Recommendation) (Arber et al., 2017)

European Hematology Association (EHA)/European Society for Medical Oncology (ESMO)

In a 2021 guideline addressing the diagnosis, treatment and follow-up for multiple myeloma, EHA and ESMO (Dimopoulos et al.) made recommendations for both newly diagnosed individuals and also those with relapsed or refractory disease noting the introduction of the use of MRD in response criteria. The authors indicate that MRD may be used as a surrogate endpoint for progression free survival for individuals receiving first-line treatment and as an endpoint for speeding up drug development. The guideline indicates that cytogenetics including karyotype and FISH are necessary at diagnosis as well as BM cytology and biopsy and next-generation flow cytometry (NGF) or NGS.

European Society for Medical Oncology (ESMO)

In a 2021 clinical practice guideline, ESMO provided recommendations on the management of CLL (Eichhorst et al.) This guideline recommends cytogenetics and molecular genetics for TP53 mutation or del(17p)and indicates that bone marrow biopsy and MRD should be carried out to identify complete remission and MRD status within clinical trials. MRD assessment is generally not recommended for monitoring after therapy outside of clinical studies at this time.

ESMO also published a clinical practice guideline addressing myelodysplastic syndromes (MDS) in 2021 (Fenaux et al.), indicating that acquired molecular mutations are found in 80%-90% of individuals with MDS and 40% of individuals with MDS have more than one mutation. Established diagnostic methods for MDS include peripheral and differential blood counts, cytomorphology of peripheral blood and bone marrow smears and cytogenetics of bone marrow cells. Molecular profiling can be a valuable diagnostic tool if MDS is uncertain, but in most cases, mutations have limited impact on management of in the majority of cases.

Heuser et al. (2020) addressed diagnosis, treatment and follow up in an ESMO practice guideline focused on care of adults with AML. The guideline recommends prompt cytogenetic and molecular evaluation to assess risk and potential treatment options and assessment of MRD at diagnosis (to establish aberrant marker profile), after 2 cycles of chemotherapy and after treatment

ends. Additionally MRD may be assessed approximately every 3 months (bone marrow) or every 4-6 weeks (peripheral blood) after the end of treatment for 24 months when individual has a molecular marker.

A clinical practice guideline from ESMO (Hoelzer et al., 2016) addressed diagnosis, treatment, and follow-up of ALL in adult patients, noting mandatory use of cytogenetics for when diagnosing ALL. The use of MRD quantification and risk classification was also noted as a necessary step in diagnostic workup and response evaluation.

National Comprehensive Cancer Network (NCCN)

Acute Lymphoblastic Leukemia (ALL)

NCCN guidelines for ALL recommend molecular characterization using fluorescence in situ hybridization (FISH) testing, reverse transcriptase-PCR testing *BCR-ABL1* in B-ALL and comprehensive NGS-based testing for gene fusions and pathogenic mutations. Optional tests include CMA in cases of aneuploidy or inadequate karyotype. Regarding MRD, NCCN recommends sensitivity of 10^{-4} or better, asserting that MRD quantification is an essential part of the evaluation of individuals with ALL through the course of sequential ALL treatment(s). In both children and adults, a meaningful association between the presence of MRD during remission and the risk of relapse has been demonstrated; MRD also has prognostic significance after induction and consolidation therapies. For both adult and pediatric ALL, the NCCN guidelines describe the timing of MRD assessment to be upon completion of initial induction, at the end of consolidation and at additional time points determined by the treatment regimen used. In addition, for some techniques, a baseline MRD assessment may be required. In individuals with molecular relapse or persistent low-level disease burden, serial monitoring frequency may be increased. (NCCN Acute Lymphoblastic Leukemia, v1.2023, NCCN Pediatric Acute Lymphoblastic Leukemia, v2.2023).

Acute Myeloid Leukemia (AML)

The NCCN guidelines for AML indicate that multiplex gene panels and targeted NGS analysis are indicated for ongoing management of AML and varying phases of treatment. Additionally, for AML relapse CGP is recommended to determine mutation status of actionable genes. Regarding MRD, the guidelines indicate that the role of MRD is evolving in both prognosis and treatment and that clinical trial participation is encouraged. MRD is listed as a component in the course of sequential therapy and the most commonly used methods for MRD assessment include PCR and multicolor flow cytometry(MFC) assays designed to detect abnormal MRD immunophenotypes. NGS assays for detection of mutated genes is not used routinely since PCR and flow cytometry yield superior results. Timing of MRD assessment in AML is at completion of initial induction, before allogeneic hematopoietic cell transplantation, and at additional time points as guided by the treatment path (NCCN Acute Myeloid Leukemia, v3.2023).

Chronic Lymphocytic Leukemia (CLL)

Per the NCCN guideline for CLL/small lymphocytic lymphoma, evidence provided by clinical trial data indicates that undetectable MRD in peripheral blood after the completion of treatment is a key predictor of the effectiveness of therapy. Although 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 $10^{-}5$, NGS based assays have been shown to offer greater sensitivity, allowing detection of MRD to the level of $10^{-}6$. The guideline states that MRD assessment should be used with an assay that has a sensitivity of $10^{-}4$, according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method. In addition, the guideline specifies that MRD detection can be performed using either blood or bone marrow and references an FDA-approved commercial NGS assay(clonoSEQ, Adaptive Biotechnologies) that allows for detection of MRD at the level of 10—6.9 (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, v3.2023).

Myelodysplastic Syndromes (MDS)

The use of gene panels including at least the 21 most frequently mutated MDS related genes to assess for MDS-associated mutations (either bone marrow or peripheral blood cells) is endorsed by the NCCN in the v1.2023 guideline for myelodysplastic syndromes. Because commercially available tests differ in specific genes analyzed, it is critical to consider the underlying indication and the area of expertise of the laboratory when selecting test panel/laboratory. Notably, genetic testing performed to identify somatic mutations in malignant cells is typically not designed to detect germline mutations, so may be inadequate to identify any underlying heritable hematologic malignancy predisposition syndrome. For individuals with relapse after allo-hematopoietic cell transplant (HCT), repeat molecular testing to identify targetable mutations is recommended (NCCN Myelodysplastic Syndromes, v1.2023).

Myeloproliferative Neoplasms

The NCCN guideline for myeloproliferative neoplasms (v1.2023) recommends molecular testing via blood or bone marrow for specific gene mutations including *J*AK2 V617F, CALR and MPL and JAK2 exon 12 mutations or a multigene panel including these genes during initial workup for individuals suspected of having a myeloproliferative neoplasm.

Multiple Myeloma

NCCN clinical practice guidelines for multiple myeloma state that single nucleotide polymorphism array or next generation sequencing panels on bone marrow have the potential to provide further risk categorization which may add prognostic value. No patient selection criteria were provided. The NCCN Multiple Myeloma Panel suggests consideration of baseline clone identification and obtaining an aspirate sample for future MRD assessment via NGS as well as assessment for circulating plasma cells in the peripheral blood (NCCN Multiple Myeloma, v3.2023).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia.
(Accessed May 22, 2023)

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Policy History/Revision Information

Date	Summary of Changes
05/01/2024	**Application** ***Louisiana*** • Updated reference link to reflect current title for state-specific policy version

03/01/2024	**Title Change/Template Update**
	• Relocated and reformatted content previously included in the Medical Policy titled *Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions*
	Related Policies
	• Added reference link to the Medical Policy titled:
	  ○ *Molecular Oncology Companion Diagnostic Testing*
	  ○ *Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions*
	Coverage Rationale
	• Revised language to indicate:
	  ○ The use of multigene panels (50 genes or fewer) at initial diagnosis and/or recurrence or relapse is proven and medically necessary when ordered by a hematologist or oncologist for individuals with:
	  ▪ Acute lymphoblastic leukemia
	  ▪ Acute myeloid leukemia
	  ▪ Multiple myeloma
	  ▪ Myelodysplastic syndrome or myeloproliferative neoplasm is strongly suspected (as evidenced by order from hematologist/oncologist)
	  ○ The use of Comprehensive Genomic Profiling (CGP) in an individual with relapsed/recurrent acute myeloid leukemia is proven and medically necessary (e.g., FoundationOne® Heme)
	  ○ Clonality assessment with clonoSEQ® Clonality ID at initial diagnosis and Measurable Residual Disease (MRD) testing with clonoSEQ® MRD are proven and medically necessary when ordered by a hematologist or oncologist for individuals with:
	  ▪ Acute lymphoblastic leukemia
	  ▪ Multiple myeloma

Date	Summary of Changes
	○ Due to insufficient evidence of efficacy, all other molecular testing for hematologic cancer is unproven and not medically necessary; for companion diagnostic testing, refer to the Medical Policy titled *Molecular Oncology Companion Diagnostic Testing* **Definitions** ● Added definition of: ○ Measurable Residual Disease (MRD) ● Removed definition of: ○ Chromosome Microarray Analysis (CMA) ○ Comparative Genome Hybridization (CGH) ○ Favorable Intermediate-Risk Prostate Cancer ○ Gene Expression Profiling (GEP) ○ Liquid Biopsy ○ Low-Risk Prostate Cancer ○ Predictive Molecular Markers ○ Prognostic Molecular Markers ○ Very Low-Risk Prostate Cancer ○ Whole Exome Sequencing (WES) ○ Whole Genome Sequencing (WGS) **Applicable Codes** ● Updated list of applicable CPT codes to reflect/include 0017M, 0050U, 0120U, 0171U, 0285U, 0296U, 0331U, 0364U, 81450, 81451, 81455, 81456, 81479, and 81599 ● Removed list of applicable ICD-10 diagnosis codes **Supporting Information** ● Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information ● Archived previous policy version CS152.X

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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