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

Policy Number: 2026T0652H
Effective Date: August 1, 2026

Instructions for Use

Table of Contents **Page**

Application 1
Coverage Rationale 1
Medical Records Documentation Used for Reviews 2
Definitions 2
Applicable Codes 2
Description of Services 4
Clinical Evidence 4
U.S. Food and Drug Administration 13
References 13
Policy History/Revision Information 15
Instructions for Use 15

Related Commercial Policies

- FDA Cleared or Approved Companion Diagnostic Testing
- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions

Community Plan Policy

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

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

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 any of the following:

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

The use of Comprehensive Genomic Profiling (CGP) (e.g., FoundationOne® Heme, Neo Comprehensive™ – Heme Cancers, NEO AML Express™) is proven and medically necessary for individuals with any of the following:

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myelodysplastic syndrome
- Myeloproliferative neoplasm

Clonality assessment with clonoSEQ® at initial diagnosis and MRD assessment with clonoSEQ® are proven and medically necessary when ordered by a hematologist or oncologist for individuals with any of the following:

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- Acute lymphoblastic leukemia
- Multiple myeloma
- Chronic lymphocytic leukemia

The use of molecular tests other than clonoSEQ® is unproven and not medically necessary for initial clonality assessment or for assessment of MRD.

Due to insufficient evidence of efficacy, all other molecular test panels for hematologic cancer are unproven and not medically necessary. This includes but is not limited to the following:
- Optical genome mapping
- Whole transcriptome sequencing

For companion diagnostic testing, refer to the Medical Policy titled FDA Cleared or Approved Companion Diagnostic Testing.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Comprehensive Genomic Profiling (CGP): A type of Next-Generation Sequencing (NGS) 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 or cell contents detectable in the body during and after cancer treatment, even though the affected individual has no signs or symptoms of disease. These cells or genetic material are not detectable through routine screening techniques or cellular morphology assessment. Residual evidence of cancer in the body of an individual that has undergone cancer treatment can be associated with earlier relapse or recurrence of disease. MRD measurement is most often used for blood cancers and can help providers form treatment plans and determine if the treatment is effective. Current assessments of MRD use real-time quantitative polymerase chain reaction (PCR), multiparametric flow cytometry and/or NGS [National Cancer Institute (NCI) Dictionary of Cancer Terms, 2025a; Yu et al., 2023].

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 the member specific benefit plan document 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
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

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CPT Code	Description
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
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
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
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations
0485U	Oncology (solid tumor), cell-free DNA and RNA by next-generation sequencing, interpretative report for germline mutations, clonal hematopoiesis of indeterminate potential, and tumor-derived single-nucleotide variants, small insertions/deletions, copy number alterations, fusions, microsatellite instability, and tumor mutational burden
0560U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood and tumor tissue, baseline assessment for design and construction of a personalized variant panel to evaluate current MRD and for comparison to subsequent MRD assessments
0561U	Oncology (minimal residual disease [MRD]), genomic sequence analysis, cell-free DNA, whole blood, subsequent assessment with comparison to initial assessment to evaluate for MRD
0644U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, blood or bone marrow, personalized assay design and baseline quantification
0645U	Oncology (leukemia), minimal residual disease (MRD) detection for rearrangements, based on digital PCR, blood or bone marrow, reported as not detected or detected with estimated abundance
81195	Cytogenomic (genome-wide) analysis, hematologic malignancy, structural variants and copy number variants, optical genome mapping (OGM)
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

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CPT Code	Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis

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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 [National Cancer Institute (NCI), Dictionary of Cancer Terms, 2025b]. 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).

Clinical Evidence

Multi-Gene Panel Use in Hematological Cancers

To ascertain the clinical utility of myeloid panel next-generation sequencing (NGS), Soderquist et al. (2024) evaluated ordering practices, prior authorization requirements, clinical impact, and reimbursement outcomes related to 477 individuals with known or suspected myeloid malignancies that underwent testing with either a 50-gene myeloid NGS panel or a 15-gene myeloproliferative neoplasm subpanel. The researchers determined that 98% (496/505) of all test outcomes afforded helpful clinical data; specifically, 89% of results either led to a diagnosis or clarified a potential diagnosis, 94% provided information regarding possible prognoses, and 19% detected a potential therapeutic target. The authors assert that their study results show that the use of a broad NGS panel significantly improves diagnostic and prognostic yield when compared to limited testing of individual genes such as *JAK2*, *CALR*, and *MPL* and add to the existing evidence supporting the broad clinical usefulness of NGS tests in individuals with myeloid neoplasias.

A 2023 Hayes Molecular Test Assessment (updated 2024) evaluated the use of FoundationOne Heme® (Foundation Medicine) to inform therapeutic options for individuals with hematologic malignancies as well as sarcomas and solid tumors. Five studies addressing clinical validity were identified. These studies, though of lower quality, showed that 32% to 90% of individuals had potentially actionable alterations detected by FoundationOne Heme. Three of the five studies reported actionable alterations that were targetable by on-label FDA-approved drugs (6% to 14% of subjects), off label FDA approved drugs (49% to 56% of subjects) or experimental drugs in a clinical trial (11% to 33% of subjects). FoundationOne Heme was not compared to other tests (such as targeted tests) or other methodologies, nor was its use in identifying therapeutic options it evaluated for clinical outcomes. One very poor quality study addressing clinical utility for FoundationOne Heme was identified, but it focused on individuals with sarcoma. The 2024 annual review of this report found no newly published studies meeting inclusion criteria.

HM-SCREEN-Japan 01 was a multicenter study of prospective genomic profiling in individuals with either newly diagnosed acute myeloid leukemia (AML) or relapsed/refractory AML who were ineligible for standard therapy (Hosono et al., 2023; included in the 2023 Hayes Molecular Test Assessment described above). The researchers used paraffin embedded bone marrow clot specimens to perform NGS using FoundationOne Heme, which incorporated sequencing of DNA from 437 genes and RNA from 265 genes. The study's purpose was to evaluate for the presence of molecular abnormalities that could potentially be targeted with novel treatment options. A total of 188 individuals from 17 institutions in Japan were enrolled; genetic alterations were identified in 177 participants (97.3%) and fusion transcripts were identified in 23.2% of participants, demonstrating the feasibility of using BM clot specimens. Both common fusion products (*RUNX1 RUNX1T1, KMT2A*) and rare rearrangements (*NUP98*)/rare fusion genes were identified. *KIT* and *WT1* mutations emerged as independent predictors of poorer overall survival and participants harboring *TP53* mutations with variant allele frequency ≥ 40% had markedly poor prognosis. In this study, FoundationOne Heme identified actionable mutations (*FLT3 ITD/TKD, IDH1/2, DNMT3A^R822*) in 38% (n = 69) of the participants, supporting targeted therapy selection in a relatively substantial subset. Overall, the authors concluded that genomic profiling using paraffin embedded bone marrow clot specimens is both practical and clinically informative, facilitating the detection of somatic mutations and potentially targetable alterations even in situations where fresh bone marrow samples are not available. Several of the authors of the publication had affiliations with laboratories associated with genetic tests and one author was a representative of the laboratory that manufactures the test used in this study (FoundationOne Heme). Notably, the median

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turnaround time for results was approximately 13 days, which may be too long to wait for results when urgent treatment decisions are needed.

In a 2018 multicenter study including 2035 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 genes had driver mutations in at least five individuals, with *JAK2*, *CALR,* or *MPL* as the only abnormality detected 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 better support individuals diagnosed with myeloproliferative neoplasms.

Weinhold et al. (2016) reported clinical outcomes of gene expression profiling (GEP) in relation to treatment type for subgroups of individuals (n = 1217) 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 risk-predicting test enabled the reliable identification of individuals with shorter durations of complete remission, event-free survival, and overall survival that constitute 10-15% of individuals with newly diagnosed MM. The authors indicated that the impact of treatment differs between molecular subtypes of MM and indicated that GEP gives important information that can help in clinical decision-making and treatment selection. They go on to recommend future studies investigating additional molecular approaches such as optical genome mapping and long-range whole genome sequencing.

Detection of Measurable Residual Disease (MRD) in Hematologic Cancers

Rios-Olais et al. (2024) investigated the prognostic value of measurable residual disease (MRD) in CLL in a recent systematic review and meta-analysis. The evaluation was comprised of only prospective trials (n = 11) reporting progression free survival (PFS) by MRD status; MRD was assessed via varying highly sensitive techniques (e.g., 10^{-4} or one per 10,000 cells), including multiparameter flow cytometry (MFC), allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), and NGS. A total of 2765 individuals that had undergone treatment with targeted therapies or obinutuzumb-based regimens were included. Results of the analysis revealed that participants who achieved an undetectable MRD had significantly longer 24-month PFS than those with detectable MRD [91.9% (95% CI, 88.8%-95.2%) vs 75.3% (95% CI, 64.7%-87.6%); $p < .001$]. This was particularly evident in the first-line treatment setting as well as with time-limited therapies. However, the use of different MRD detection methods and tissues (with varied sensitivity and specificity) could impact direct comparison and potentially affect reliability of pooled results. In addition, the timing of MRD assessment was variable across studies, and some trials did not test for MRD unless the participant achieved a complete response, which introduces bias. Lastly, the study was restricted to specific therapy types and the majority of studies focused on PFS rather than overall survival (OS), which is a more definitive clinical outcome. Despite these limitations, the authors determined that based on their large systematic review and meta-analysis, MRD status is strongly associated with PFS in individuals with CLL and support the use of MRD as a surrogate endpoint in the setting of clinical trials. They advocate for the standardization of MRD assessment in both research and clinical practice.

The measurement of MRD played a central role in guiding treatment decisions for participants with relapsed/refractory CLL in the CLL2-BZAG trial (Fürstenau et al., 2025). CLL2-BZAG was a phase 2 trial which enrolled 42 participants (two were excluded per study protocol) with relapsed/refractory CLL who received treatment with zanubrutinib, venetoclax, and obinutuzumab after optional bendamustine debulking; the duration of therapy was tailored based on MRD status (determined via high-sensitivity flow cytometry). MRD assessment occurred at regular intervals for tracking depth of response and to guide treatment cessation. Participants had a median of one prior treatment (range = one to five treatments). Fifteen of the participants had a *TP53* mutation/deletion and 31 had unmutated immunoglobulin heavy chain variable region gene (high risk genetic features). After six months of triple therapy, 100% of participants responded, with 52.5% [95% confidence interval (CI), 36.1-68.5] achieving undetectable MRD in peripheral blood. Estimated 18-month PFS was 96% and estimated eighteen-month OS was 96.8%. In addition, no participants required further treatment during the observation period (median 21.5 months) and over time, undetectable MRD deepened; maximum undetectable MRD rate was 85% for the entire study population. Of note, COVID-19 had an impact on this study, affecting 26 of the 42 participants, with two COVID-19-related deaths. The study was limited by its small sample size and the prior bendamustine debulking treatment of half of the participants, as well as the presence of high-risk features in a significant proportion of participants. Two participants with very early treatment discontinuations were excluded; this exclusion may

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have led to overestimation of the efficacy of the study treatment. In addition, MRD was measured primarily in peripheral blood, which may not fully reflect disease status in bone marrow or lymphoid tissues. Despite the limitations, the trial demonstrated high response rates and deep MRD remissions. The researchers suggest that the results of this study, in which the use of MRD measurements were vital, show promise for the use of an MRD-guided approach to treatment with zanubrutinib, venetoclax, and obinutuzumab as it resulted in deep remissions, high response rates, and durable disease control, even in participants previously treated with BTK inhibitors or venetoclax and/or with high-risk genetics, and allowed for time-limited treatment, which reduces potential toxicity.

Munir et al. (2024) examined the use of MRD in the context of a phase three, multicenter (96 facilities), randomized controlled trial in the United Kingdom (FLAIR; ISRCTN01844152). Initially, the FLAIR trial compared ibrutinib plus rituximab with fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated participants with CLL, but in 2017, the trial was adapted to include both ibrutinib alone and ibrutinib–venetoclax with the length of therapy determined according to MRD testing results. Participants were randomized to receive FCR, ibrutinib monotherapy, or ibrutinib-venetoclax . The key outcome in the comparison between MRD-guided ibrutinib-venetoclax and FCR was progression-free survival, which was defined as duration of time from randomization to progression of disease or death. A total of 523 individuals (260 in the ibrutinib–venetoclax group and 263 in the FCR group) were evaluated in this cohort. After median time of 43.7 months, death or progression of disease had occurred in 12 participants in the ibrutinib-venetoclax group and 75 participants in the FCR group [hazard ratio (HR), 0.13; 95% CI, 0.07 to 0.24; $p < 0.001$]. The risk of infection was similar in both groups, but the percentage of participants with serious cardiac adverse events was higher in the ibrutinib-venetoclax group than in the FCR group (10.7% vs. 0.4%). The researchers concluded that MRD-guided ibrutinib–venetoclax outperformed FCR in terms of both progression-free survival (97.2% vs. 76.8% at 3 years) and overall survival (98.0% vs. 93.0% at 3 years). In those individuals who tend to have poorer outcomes with standard treatments (e.g., individuals with unmutated *IGHV* and certain other genetic abnormalities), MRD-guided ibrutinib-venetoclax benefits were especially evident. Although this data appears promising, the use of MRD testing in individuals with CLL is still the subject of some debate. Previous trials found differing results in terms of undetectable MRD and survival rates (Hillmen et al., 2023; Shanafelt et al., 2022).

CLL14 was an open-label, randomized, phase-three trial of 432 participants with previously untreated CLL who underwent therapy with either venetoclax-obinutuzumab (Ven-Obi, 216 patients), or chlorambucil- obinutuzumab (Clb-Obi, 216 patients). The primary endpoint was PFS; secondary endpoints were MRD status (measured by NGS) and OS. In a 2023 publication, Al-Sawaf et al. reported the five-year results from CLL14. The study showed substantially better PFS for Ven-Obi compared to Clb-Obi, with estimated PFS five years after randomization at 62.2% vs 27%, respectively. MRD response was defined as end-of-treatment MRD status $< 10^{-6}$ in peripheral blood and MRD non-response was defined as end-of-treatment MRD status $\geq 10^{-4}$ in peripheral blood. Both arms of the trial demonstrated that participants with MRD negativity ($< 10^{-6}$) at the end of treatment had longer PFS than those with detectable MRD (Ven-Obi: HR 0.25, 95% CI 0.14–0.47; Clb-Obi: HR 0.06, 95% CI 0.02–0.25). Notably, MRD positive ($\geq 10^{-4}$) results were associated with higher expression of the multiple-drug resistance gene *ABCB1 (MDR1)* while MRD6 negativity ($< 10^{-6}$) was associated with *BCL2L11 (BIM)* expression. The results suggest that Ven-Obi may provide sustained long-term efficacy and deeper remission in comparison to Clb-Obi and additionally, bolster the body of evidence supporting the use of MRD testing to help identify individuals who are likely to remain in remission versus those who may be at risk of relapse. Although this study found MRD to be a strong prognostic factor, gene expression patterns associated with MRD negativity did not consistently predict long term outcomes. In addition, subgroup analyses were limited by small sample sizes and there was significant variability in GEPs among participants, making it somewhat difficult to identify consistent biomarkers for treatment response. The authors suggest dedicated randomized studies that focus on the long-term benefits of MRD-guided treatment compared to continuous or fixed-duration treatment.

Costa et al. published the final report of the completed MASTER trial (NCT03224507) in 2023. MASTER was a phase two, single-arm, multi-center trial performed in the United States. To be enrolled, participants met inclusion criteria consisting of: 1) 18 years of age or older, 2) newly diagnosed MM, 3) life expectancy of at least 12 months, 4) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and 5) no prior treatment for MM received, with the exception of one cycle of bortezomib, cyclophosphamide, and dexamethasone. The researchers enriched the study for individuals with high-risk chromosome abnormalities (HRCAs) and a total of 123 individuals with median age of 61 years were included. The primary outcome of the study was the achievement of negative MRD ($< 10^{-5}$) For induction, each participant was treated with four 28-day cycles of daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd). After the induction phase of treatment, participants received autologous haematopoietic stem-cell transplantation and no more than two additional phases of consolidation with Dara-KRd. During or after each phase of treatment, MRD was evaluated via NGS. If a participant attained MRD-negative results after or during the course of the two additional phases of therapy, Dara-KRd treatment was discontinued and observation, including MRD measurement, commenced (MRD-SURE). If a participant did not attain two consecutive MRD-negative findings, maintenance therapy with lenalidomide was started. Also assessed in this trial was progression-free survival and cumulative occurrence of

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progression. Five participants had insufficient unique clonogenic sequences to allow tracking by the assay used; of the remaining 118 participants, 96 achieved MRD of less than 10^{-5} (81%, 95% CI 73–88). This included 78% of individuals who had no HRCAs, 86% of individuals with one HRCA, and 79% of individuals with two or more HCRAs. Overall, 71% of participants (n = 84) reached MRD-SURE, ending treatment. Of those 84 participants, the cumulative incidence of progression from the time therapy ended was 9% (95% CI 1–19) for participants with no HRCAs, 9% (1–18) for those with one HRCA, and 47% (23–72) for those with two or more HRCAs. Fifty-two percent of total MRD evaluable study enrollees (including 52% of 118 MRD-evaluable enrollees and 73% of 84 participants who achieved MRD-SURE) continued to be MRD-negative and therapy-free as of Feb 7, 2023. The authors concluded that MRD response-adapted treated yielded positive outcomes and defined a potential pathway for therapy termination in the majority of individuals with newly diagnosed MM. However, individuals with very high risk MM (two or more HRCAs) did not achieve satisfactory outcomes and additional study is required to determine the best treatment options in these circumstances.

To assess the clinical impact of using a very sensitive NGS MRD assay (clonoSEQ) in adults with acute lymphocytic leukemia (ALL) receiving frontline therapy, Short et al. (2022) performed a retrospective study of 74 individuals from a single center in Texas undergoing treatment with either hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (hyper-CVAD) or hyperfractionated cyclophosphamide, vincristine and dexamethasone alternating with methotrexate and cytarabine (mini–hyper-CVD) with complete remission (CR) achieved as best response after one cycle of induction therapy. CR was defined as five percent or fewer blasts in the bone marrow with absolute neutrophils of at least 1 x 10^9/L and a platelet count of at least 100 x 10^9/L. For this study, the researchers defined “relapse” as recurrence of bone marrow blasts greater than 5% or extramedullary ALL. When remission samples that were determined to be MRD negative by MFC were assessed with the more sensitive NGS assay, 46% were found to be MRD positive. After a cycle of induction therapy, 66% of participants were found to be MRD negative via testing with MFC (sensitivity of 1 x 10^{-4}), while only 23% of participants were MRD negative by NGS (sensitivity of 1 x 10^{-6}). Of participants who reached MRD negativity per MRC at CR, the five-year cumulative incidence of relapse (CIR) was 29%. When early MRD negativity was determined via NGS, no participants relapsed and overall survival at five years was 90%. Risk of relapse was significantly reduced when MRD was deemed negative versus positive with the NGS MRD test (5-year CIR, 0% vs 45%, respectively; p = .04). When participants had a negative MRD result per MFC but levels of MRD were detected with the NGS test, participants still had a substantial risk of relapse (5-year CIR, 39%). Although the study was retrospective and the number of participants was low, the authors contend that use of a highly sensitive NGS assay for MRD assessment in individuals undergoing frontline therapy for ALL can lead to detection of a substantial portion that had been deemed MRD-negative per standard MFC testing but still have an unacceptable rate of relapse. This, in turn, provides improved prognostic data for affected individuals and may be leveraged for the identification of individuals who are at very low risk of relapsed disease.

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 individuals 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 2024].

Pulsipher et al. (2022, included in the Hayes 2022 Molecular Test Assessment) sought to define biomarkers predictive of relapse by evaluating MRD detection and B-cell aplasia in individuals with 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 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 NGS in BM was significantly associated with relapse. If B-cell recovery occurred within the first year of treatment, HR for relapse was 4.5 (95% CI, 2.03 - 9.97; p < 0.001). Measured on 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. After 3 months from treatment start, 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. For

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this evaluation, 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 individuals with RRMM who received ≤ 2 prior lines of therapy (≤ 2 PL); 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 five-year OS for the MRD-negative group was 67% [95% Bayesian credible interval (CrI), 53-77%] and for the 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, currently MRD assays for AML could 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 DFS of 63% indicates that a significant portion of MRD-negative individuals will still relapse. In contrast, a small percentage (16%) of individuals who were MRD-positive were still disease free at 5 years. Based on the results of their analysis, the authors concluded that for individuals with AML in remission, MRD-negativity correlates with higher rates of DFS and OS, which provides support for the use of MRD measurement to aid with regulatory decision-making and serve as a surrogate marker for survival in individuals with AML.

A 2021 NICE innovation briefing states that the clonoSEQ test for assessment of MRD in individuals with multiple myeloma, ALL, and CLL 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 base at this time.

Wierda et al. (2021) published an expert review and consensus recommendations addressing the use of MRD to evaluate disease burden during and after treatment of CLL. The authors noted 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 included in the 2022 Hayes Molecular Test Assessment above, 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 noting 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, advising that

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for 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 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 note 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 OS in individuals with CLL after upfront chemotherapy or chemo-immunotherapy was published by Molica et al. in 2019. A total of eleven studies were included overall; nine provided information on PFS, and six provided information on OS. Substantial differences between the 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 ($p < .001$). 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, included in the 2022 Hayes Molecular Test Assessment) 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 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 for the detection of MRD in individuals with AML was studied by Jongen-Lavrencic et al. (2018). Between 2001 and 2013, a total of 482 individuals with newly diagnosed AML ranging in age from 18 to 65 years were included. NGS of 54 genes that are often present in individuals with AML was performed at diagnosis and after induction therapy during complete remission. The primary outcomes analyzed were four-year relapse, relapse-free survival, and OS. Results were compared with MRD results using flow cytometry (FC). The authors discovered an average of 2.9 mutations per individual, and at least one single mutation with the potential to be an indicator of residual disease was found in 89.2% of participants (n = 430) at the time of diagnosis. NGS testing was repeated on bone marrow after induction therapy; persistent mutations were found in 51.4% and the rate of mutation was highly variable across the genes analyzed. *DTA* mutations were most common, persisting at rates of 78.9%, whereas *RAS* pathway mutations commonly cleared after induction therapy, persisting at an average rate of about 9%. The authors noted that *DTA* mutations are commonly found 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 (55.4% vs. 31.9%), lower relapse-free survival (36.6% vs. 58.1%), and lower OS (41.9% vs. 66.1%). The results of NGS were compared to FC in a subset of 340 individuals. Concordant results for detection or non-detection of MRD were found in 69% of those individuals. The four-year rate of relapse was 73.3% among participants in whom both assays were positive, 52% among those who had residual disease per NGS but not on FC, 49.8% among those who had residual disease on FC but not on NGS, and 26.7% among those in whom both assays were negative. Multivariate analysis found that combining the two assays yielded independent prognostic value to the rate of relapse ($p < 0.001$), relapse free survival ($p < 0.001$) and OS ($p = 0.003$).The authors concluded that persistent mutations associated with clonal hematopoiesis did not have prognostic value related to relapse/survival, whereas the detection of MRD during complete remission using NGS in addition to FC had significant added 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 individuals with ALL, in an ongoing study of 323 individuals with MM, and in a separate study of 706 individuals with MM. Affected individuals with negative MRD results had 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 ongoing CLL14 study (NCT02242942) demonstrated that participants with an undetectable MRD (blood) per the clonoSEQ test had an almost seven-fold reduction in risk of

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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 had an undetectable MRD, versus 36% in 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 MFC or ASO-PCR. The analytical sensitivity for FC is approximately 0.01%; ASO-PCR is 0.001% but requires the development of specific probes for each individual. Wood et al. (2018) compared the clinical validity of a new technical approach of using high throughput sequencing (HTS) of *IGH* and *TRG* genes to FC for determining MRD. The study used 619 paired pretreatment and end-of-induction bone marrow samples from Children's Oncology Group studies AALL0331 and AALL0232 (NCT00103285 and NCT00075725, respectively). The samples were evaluated by HTS and FC for event free survival and OS. Using an MRD threshold of 0.01%, HTS and FC showed similar 5-year event free survival and OS rates, but there was high discordance between HTS and FC in number of MRD-positive individuals identified; HTS identified 55 more individuals as MRD positive (39%) and these individuals had worse outcomes than individuals with FC MRD negative results. HTS also identified 19.9% of affected individuals at standard risk without MRD at any detectable level, which correlated with excellent outcomes. Overall HTS had a high sensitivity and lower false-negative rate than FC in this analysis.

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 (MM). 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 individuals who are transplant-eligible 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 affected individuals 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)/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 AML (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).

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- "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 care for MM, 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.

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 an individual has a molecular marker.

A clinical practice guideline from ESMO (Hoelzer et al., 2016) addressed diagnosis, treatment, and follow-up of ALL in adults, noting mandatory use of cytogenetics 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 FISH testing (including probes capable of identifying the major recurrent genetic abnormalities), reverse transcriptase PCR testing to measure transcript sizes of *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 validated MRD assessment technology with 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). The most commonly used technology for MRD quantification includes FDA-approved NGS-based assays for detection of fusion genes or clonal rearrangements in Ig and T-cell receptor loci, flow cytometry assays designed to detect abnormal MRD immunophenotypes at low frequency, real- time quantitative PCR (RQ-PCR) assays and reverse transcriptase quantitative PCR (RT-qPCR) assays (e.g., BCR/ABL1). If MRD is determined to be negative by flow cytometry, an FDA-approved NGS assay is recommended for consideration to confirm negativity. 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 and risk features. In addition, for some techniques, a baseline MRD assessment may be required. In individuals with molecular relapse or persistent low-level

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disease burden, serial monitoring frequency may be increased. (NCCN Acute Lymphoblastic Leukemia, v2.2025; NCCN Pediatric Acute Lymphoblastic Leukemia, v5.2024).

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, molecular profiling is recommended to determine the mutation status of actionable genes. Regarding MRD, the guidelines suggest that there is compelling evidence indicating that detectable MRD following remission is associated with an increased risk of relapse in both adults and children. However, the role of MRD testing as it relates to both prognosis and treatment of AML is evolving and the addition of MRD assessment into routine practice has presented challenges due to lack of standardization and established cut-off values. Ongoing research is investigating these limitations; the NCCN panel notes that participation in clinical trials is encouraged. Standard NGS testing is not designed for MRD assessment due to its inferior sensitivity. The most commonly used methods for assessment of MRD include real-time quantitative PCR and multicolor flow cytometry (MFC) assays designed to detect abnormal MRD immunophenotypes. Although the evidence addressing optimal frequency and timing of MRD assessment in AML is limited, the NCCN panel recommends monitoring upon achievement of morphologic remission, at the time of and following allogeneic hematopoietic cell transplantation (HCT), after two cycles of intensive chemotherapy for *NPM1*-mutated AML, every three months for at least 2 years for *PML;RAR* alpha in acute promyelocytic leukemia (APL), and at additional time points guided by the specific treatment program used. (NCCN Acute Myeloid Leukemia, v2.2025).

Chronic Lymphocytic Leukemia (CLL)

Per the NCCN guideline for CLL/small lymphocytic lymphoma, the use of FISH for the detection of +12; del(11q); del(13q); del(17p), TP53 sequencing, CpG-stimulated metaphase karyotyping for complex karyotypes, and molecular analysis for the identification of immunoglobulin heavy chain variable region gene (IGHV) mutation status is helpful for prognostication and for treatment determination. Regarding MRD assessment, evidence provided by clinical trial data indicates that undetectable MRD in peripheral blood at the end of fixed duration 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} (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, v3.2025).

Myelodysplastic Syndromes (MDS)

The use of gene panels including the genes most frequently somatically mutated in MDS (either bone marrow or peripheral blood cells) is endorsed by the NCCN in the v2.2025 guideline for myelodysplastic syndromes. These genetic mutations can detect the presence of clonal hematopoiesis (which can aid with the exclusion of benign causes of cytopenia), but do not definitively diagnose MDS in the absence of clinical diagnostic criteria. Because commercially available tests differ in specific genes analyzed, among other factors, 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. (NCCN Myelodysplastic Syndromes, v2.2025).

Myeloproliferative Neoplasms

The NCCN guideline for myeloproliferative neoplasms (v2.2025) recommends molecular testing via blood or bone marrow for specific gene mutations including *JAK2 V617F, CALR* and *MPL* and *JAK2* exon 12 mutations or a multigene NGS panel including these genes during initial workup for individuals suspected of having a myeloproliferative neoplasm. When diagnosis of myeloproliferative neoplasm is confirmed, NGS is recommended for mutational prognostication. In myelofibrosis, NGS and karyotyping of bone marrow aspirate/biopsy should be performed at diagnosis and as clinically indicated (e.g., with increasing symptoms and/or signs of disease progression). Additionally multigene panels should be considered for evaluation of higher-risk mutations that are associated with disease progression.

Multiple Myeloma

NCCN clinical practice guidelines for MM state that single nucleotide polymorphism array or NGS panels on bone marrow have the potential to provide further risk categorization which may add prognostic value. No specific selection criteria were

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provided. The NCCN Multiple Myeloma Panel recommends baseline clonotype identification at diagnosis or storage of aspirate sample for future clonotype identification to allow for MRD assessment via NGS as well as assessment for circulating plasma cells in the peripheral blood when clinically indicated (NCCN Multiple Myeloma, v2.2026).

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 July 25, 2025)

Refer to the following website for a list of nucleic acid-based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Heath: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed July 25, 2025)

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Policy History/Revision Information

Date	Summary of Changes
08/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0644U and 0645U **Supporting Information** • Archived previous policy version 2026T0652G

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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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