Healthy Blue

Clinical UM Guideline

Subject:	Detection and Quantification of Tumor DNA Using Next Generation Sequencing in Lymphoid Cancers		
Guideline #:	CG-GENE-19	**Publish Date:**	02/05/2020
Status:	New	**Last Review Date:**	11/07/2019

Description

This document addresses next generation sequencing (NGS; also known as high-throughput and deep sequencing) of tumor DNA to assist in determining the success of the treatment, forming a prognosis, monitoring disease progression and choosing therapies for individuals with lymphoid cancer.

Note: Please see the following related document for additional information:

- CG-GENE-13 Genetic Testing for Inherited Diseases
- LAB.00015 Detection of Circulating Tumor Cells in the Blood as a Prognostic Factor for Cancer

Clinical Indications

Medically Necessary:

Next generation sequencing of tumor DNA to detect or quantify measurable (minimal) residual disease in individuals with acute lymphocytic leukemia is considered **medically necessary.**

Next generation sequencing of tumor DNA to detect or quantify measurable (minimal) residual disease in individuals with multiple myeloma following transplant is considered **medically necessary.**

Not Medically Necessary:

Next generation sequencing of tumor DNA in individuals with all other lymphoid cancer is considered **not medically necessary.**

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

81479	Unlisted molecular pathology procedure [when specified as NGS tumor DNA testing for MRD, such as ClonoSEQ testing]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as NGS tumor DNA testing for MRD, such as ClonoSEQ testing]

ICD-10 Diagnosis

C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)
Z85.6	Personal history of leukemia [when specified as ALL]
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues [when specified as multiple myeloma]

Discussion/General Information

Lymphoid Cancer (Lymphoma)
Lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) is the most common type of blood cancer. Lymphoma develops when lymphocytes multiply and grow uncontrollably. The two principal types of cells that develop into lymphomas are B-lymphocytes (B-cells) and T-lymphocytes (T-cells). There are other types of B-cell NHL, including but not limited to follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), DLBCL, MM, and MCL. Lymphoblastic or lymphocytic leukemia is a related cancer and is considered either a lymphoma or leukemia, depending on how much of the bone marrow is involved.

Treatment options for lymphoma vary depending upon the disease subtype and may include surgery, radiation therapy, chemotherapy, targeted therapy, plasmapheresis, biologic therapy, stem cell transplant and watchful waiting. In certain cancers, an important consideration in determining success of treatment and monitoring disease progression and prognosis is the monitoring of MRD. Research is being done to determine if MRD detection and quantification using ctDNA can be used in managing individuals with lymphoid cancer.

Measurable (Minimal) Residual Disease Assessment in Lymphoid Cancer
While some individuals who undergo treatment for lymphoma will achieve a complete remission and experience prolonged disease-free survival, others may experience a recurrence or die from the disease. Relapse is thought to be the result of residual cancer cells that remain following a "complete" remission, but are below the limits of detection using conventional morphologic assessment. These subclinical levels of residual cancer cells, referred to as measurable residual disease (MRD, previously termed minimal residual disease [MRD]), are an important consideration in determining the success of the treatment, forming a prognosis, monitoring disease progression and choosing therapies.

Current generally accepted methods for MRD assessment include allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and flow cytometry (FC). Each technique has its advantages and disadvantages. ASO-PCR provides high sensitivity (generally 1 leukemic cell in 100,000; 0.001%) and has wide applicability given that many malignant cells in many individuals with leukemia, lymphoma, or another malignant hematologic disease have

acquired clonal chromosomal abnormalities. But ASO-PCR is time-intensive, typically requires bone marrow and the development of unique patient-specific primers and probes for quantitative PCR. FC also has wide applicability, can be accomplished within 1 day from bone marrow or whole blood and can provide information on both benign and malignant cells, but has lower sensitivity (generally 1 leukemic cell in 10,000; 0.01%). Neither ASO-PCR nor FC is capable of capturing changes associated with immunophenotypic drift during disease progression.

Research is ongoing to determine if high-throughput (deep) sequencing of circulating tumor DNA (ctDNA) to detect or quantify MRD can be used to manage individuals with lymphoid cancer. ctDNA has been identified in a variety of malignancies and levels have been shown to increase with disease stage. The analysis of ctDNA requires the use of highly sensitive techniques due to the small fraction of tumor specific DNA present within background levels of normal cell-free circulating DNA (cfDNA). Unlike PCR and FC based assays, deep sequencing allows for both the monitoring of MRD of original clones and of clonal evolution during therapy. In initial tests, deep sequencing detected one leukemic cell among greater than 1 million leukocytes. Targeted deep sequencing using PCR-based approaches have been employed to sequence specified genomic regions in blood, plasma and bone marrow (Ignatiadis, 2014).

Monitoring tumor-specific mutations in plasma following surgical resection has the potential to identify individuals at risk of relapse and to detect disease recurrence. The ability to make an early diagnosis of relapse may allow effective treatment strategies to be implemented at a time when disease burden is still minimal. Additionally, researchers are exploring the role of ctDNA in stratifying individuals at highest risk of relapse to guide the selection of the most appropriate adjuvant therapy (Ignatiadis, 2014).

Measurable (Minimal) Residual Disease Assessment in Acute Lymphocytic Leukemia (also known as Acute Lymphoblastic Leukemia [ALL])
The National Comprehensive Cancer Networks (NCCN) Clinical Practice Guidelines on Acute Lymphoblastic Leukemia (V2.2019) indicate that MRD is an essential component of the evaluation of individuals with ALL during the course of sequential therapy. According to the NCCN:

> Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate. If patient is not treated at an academic medical center, there are commercially available tests that should be used for MRD assessment. Six-color flow cytometry can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-4} (<0.01%) bone marrow MNCs, and PCT or NGS methods can detect leukemic cells at a sensitivity threshold of fewer than 1×10^{-6} (<0.0001%) bone marrow MNCs. The concordance rate for detecting MRD between these methods is generally high.

MRD status at various time points during and following treatment has prognostic value, and some studies suggest that altering therapy based on the results of MRD testing improves morbidity and mortality. While PCR-based

techniques and FC are currently employed for MRD assessment in most individuals with ALL, studies have demonstrated that MRD can be determined with accuracy using NGS.

Faham and colleagues (2012) assessed the suitability of this method to monitor MRD in individuals with ALL. The authors compared the deep sequencing method with the gold-standard MRD assays, multiparameter FC and ASO-PCR, using diagnostic and follow-up samples from 106 participants. Deep sequencing detected MRD in all 28 samples shown to be positive by FC and in 35 of the 36 shown to be positive by ASO-PCR, and revealed MRD in 10 and 3 additional samples that were negative by FC and ASO-PCR, respectively. The authors concluded that although the study was limited to "the most common form of ALL, B-lineage, the same approach could also be applied to T-lineage ALL or other lymphoid malignancies such as chronic lymphocytic leukemia, non-Hodgkin lymphoma and multiple myeloma."

Logan and colleagues (2014) used the LymphoSIGHT HTS platform (Sequenta Inc., South San Francisco, CA) to quantify MRD in 237 samples from 29 adults with B cell ALL prior to and after allo-hematopoietic cell transplantation (HCT). Using primers for the IGH-VDJ, IGH-DJ, IGK, TCRB, TCRD, and TCRG loci, MRD was quantified in 93% of subjects. Leukemia-associated clonotypes at these loci were found in 52%, 28%, 10%, 35%, 28%, and 41% of participants, respectively. MRD ≥ 10(-4) before HCT conditioning forecasted post-HCT relapse (hazard ratio [HR], 7.7; 95% confidence interval [CI], 2.0 to 30; p=0.003). In post-HCT blood samples, MRD ≥ 10(-6) demonstrated 100% positive predictive value for relapse with median lead time of 89 days (HR, 14; 95% CI, 4.7 to 44, p<0.0001). The authors concluded that the use of this technology might identify a window for clinical intervention before clinically evident relapse without reliance on bone marrow for MRD quantification.

According to the NCCN Clinical Practice Guidelines on Acute Lymphoblastic Leukemia (V1.2018) the most frequently used methods for MRD assessment include 6-color flow cytometry assays which detect abnormal immunophenotypes, RQ-PCR assays, and NGS-based assays to detect fusion genes (eg, BCR-ABL1), clonal rearrangements in immunoglobulin (Ig) heavy chain genes, and/or T-cell receptor (TCR) genes. The NCCN considers new multiplexed PCR and NGS for MRD emerging methodologies.

In September 2018, the U. S. Food & Drug Administration (FDA) granted De Novo designation for the ClonoSEQ® Minimal Residual Disease assay, (Adaptive Biotechnologies®, Seattle, WA), a next generation sequencing (NGS)-based test for MRD in patients with multiple myeloma or ALL.

Measurable (Minimal) Residual Disease Assessment in Chronic Lymphocytic Leukemia (CLL)
Logan and colleagues (2011) investigated the use of high-throughput sequencing for the quantification of MRD in 6 individuals who had undergone HCT for chronic lymphocytic leukemia (CLL). In this study, the researchers reported using widely available consensus primers (sets of primers that can be used for any subject) to amplify all immunoglobulin heavy chain (IGH) genes in a mixture of polyclonal lymphoid cells, followed by parallel high-throughput sequencing (HTS) of the resulting immunoreceptor amplimers. The goal of the study was to compare the performance characteristics of IGH-HTS, ASO-PCR, and FC for tracking disease burden in a group of CLL subjects following HCT. Using amplimer libraries generated with consensus primers from 28 blood samples of 6 individuals with CLL, the authors determined the sensitivity of IGH-HTS to be 10(-5), with a high correlation

between quantification by ASO-PCR and IGH-HTS (r=0.85). The researchers found that while the IGH–HTS approach demonstrated sensitivity equivalent to ASO-PCR, it did not require patient-specific reagents or procedures.

In 2013, Logan and colleagues used the LymphoSIGHT method, an IGH–HTS MRD platform with a validated detection limit of 10(-6) and quantitative range above 10(-5), to predict relapse in 40 study participants who had undergone reduced-intensity allo-HCT for high-risk CLL. More than 400 samples from the 40 participants were analyzed. A total of 9 participants relapsed within 12 months post-HCT. Of the 31 subjects in remission at 12 months post-HCT, disease-free survival was 86% in subjects with MRD < 10(-4) and 20% in those with MRD ≥ 10(-4) (relapse hazard ratio [HR] 9.0; 95% CI, 2.5-32; p<0.0001), with median follow-up of 36 months. Additionally, MRD predicted relapse at other time points, including 9, 18 and 24 months post-HCT. MRD doubling time < 12 months with disease burden ≥ 10(-5) was associated with relapse within 12 months of MRD assessment in 50% of subjects, and within 24 months in 90% of subjects. The authors concluded that the IGH-HTS method may facilitate routine MRD quantification in clinical trials.

Measurable (Minimal) Residual Disease Assessment in Diffuse Large B-cell Lymphoma (DLBCL)
Kurtz and colleagues (2015) explored the use of non-invasive monitoring of diffuse large B-cell lymphoma (DLBCL) by immunoglobulin high-throughput sequencing (Ig-HTS). In this prospective study, the authors evaluated the utility of NGS technique in 311 blood and 105 tumor samples from 75 individuals with DLBCL by comparing the cellular (circulating leukocytes) and acellular (plasma cell-free DNA) components of peripheral blood and 18FDG PET/CT to clinical outcomes. Clonal immunoglobulin rearrangements were identified in 83 % of subjects with adequate tumor samples to enable subsequent monitoring in peripheral blood. Molecular disease based on plasma, as compared to circulating leukocytes, was more abundant and more correlated with radiographic disease burden. Prior to treatment, molecular disease was detected in the plasma of 82 % of the subjects compared to 71 % in circulating cells (p=0.68). However, molecular disease was detected significantly more often in the plasma at time of relapse (100% vs. 30 %, p=0.001). Detection of molecular disease in the plasma often preceded PET/CT detection of relapse in subjects initially achieving remission. During surveillance time-points prior to relapse, plasma Ig-HTS exhibited improved specificity (100% vs. 56%, p<0.0001) and similar sensitivity (31% vs. 55%, p=0.4) compared to PET/CT.

In a study by Roschewski and colleagues (2015), researchers retrospectively assessed whether ctDNA encoding the clonal immunoglobulin gene sequence could be detected in serial serum samples of individuals with DLBCL and be used to predict clinical disease recurrence after frontline treatment. Clonal products were identified in the pretreatment specimens from 126 subjects who were followed for a median of 11 years. Interim monitoring of ctDNA at the end of two treatment cycles in 108 subjects demonstrated a 5-year time to progression of approximately 40% in participants with detectable ctDNA and approximately 80% in those without detectable ctDNA (p<0.0001). Detectable interim ctDNA demonstrated a positive predictive value of 62.5% (95% CI 40.6-81.2) and a negative predictive value of 79.8% (69.6-87.8). Surveillance monitoring of ctDNA was carried out in 107 of the participants who achieved complete remission. A Cox proportional hazards model indicated that the hazard ratio for clinical disease progression was 228 (95% CI, 51-1022) for individuals who developed detectable ctDNA during surveillance compared with individuals with undetectable ctDNA (p<0.0001). Surveillance ctDNA

revealed a positive predictive value of 88.2% (95% CI, 63.6-98.5) and a negative predictive value of 97.8% (92.2-99.7) and identified risk of recurrence at a median of 3.5 months (range 0-200) prior to evidence of clinical disease.

Various Lymphomas
Ladetto and colleagues (2014) compared immunoglobulin heavy-chain-gene-based MRD detection by real-time quantitative polymerase chain reaction (RQ-PCR) and NGS to assess MRD detection in individuals with B-cell disorders. A total of 378 samples from 55 participants with ALL, mantle cell lymphoma (MCL) or MM were investigated for clonotype identification, clonotype identity and comparability of MRD results. A total of 45 clonotypes were identified by RQ-PCR and 49 by NGS. Clonotypes identified by both methods were identical or > 97% homologous in 96% of cases. MRD results demonstrated a good correlation ($R=0.791$, $p<0.001$), with excellent concordance in 79.6% of cases. A small number of discordant cases were observed across all disease subtypes. NGS demonstrated at least the same level of sensitivity as ASO-PCR, without the need for patient-specific reagents. The authors acknowledged that while NGS appears to be an effective tool for MRD monitoring in ALL, MCL and MM, prospective comparative analysis of unselected cases is required to validate the clinical impact of NGS-based MRD assessment.

The NCCN Clinical Practice Guidelines on Hairy Cell Leukemia (V3. 2019) indicate "the clinical relevance of MRD status in patients with disease responding to therapy remains uncertain at this time". The guideline does not specifically address the use of NGS of ctDNA to detect or monitor MRD. NCCN Clinical Practice Guidelines on Hodgkin Lymphoma (V2.2019) do not provide criteria for MRD testing.

Definitions

Allele-specific oligonucleotide PCR (ASO-PCR): A two-step nested polymerase chain reaction (PCR) technique that allows the direct detection of any point mutation in human DNA.

Amplimer: A piece of DNA formed as the products of natural or artificial amplification events, as in a polymerase chain reaction.

Circulating tumor DNA (ctDNA): Small portions of nucleic acid that are not associated with cells or cell fragments.

Flow cytometry: A diagnostic test which identifies the arrangement and amount of DNA in a cell.

Deep sequencing: A testing strategy in which sequencing a genomic region is done multiple times, sometimes hundreds or even thousands of times, allowing the detection of rare clonal types, cells, or microbes. Deep sequencing increases the yield with low purity tumors, highly polyclonal tumors, and applications that require high sensitivity (identifying low frequency clones).

Lymphatic system: The body's network of vessels through which lymph drains from the tissues into the blood. The lymphatic system includes the lymph nodes, bone marrow, spleen and thymus gland.

Lymphocytes: Specialized white cells found in the body's immune system.

Lymphoma: A type of cancer that begins in the lymphatic system.

Measurable (minimal) residual disease (MRD): The cancer cells that may remain in the body during or following treatment. These cells are present at levels undetectable by traditional microscopic (morphologic) examination of blood, bone marrow or a lymph node biopsy.

Next-generation sequencing: Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes. This technology includes but is not limited to high-throughput (deep) sequencing.

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action

New	11/07/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of GENE.00045 Detection and Quantification of Tumor DNA Using Next Generation Sequencing in Lymphoid Cancers to new clinical utilization management guideline with same title.