August 2, 2017

Ms. Virginia Muir
LCD Comments
P.O. Box 7108
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PartBLCDComments@anthem.com

RE: Genomic Sequence Analysis Panels in the Treatment of Myelodysplastic Syndromes (MDS) (DL37078)

Dear Ms. Muir,

Thank you for the opportunity to comment on DL37078. The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the College of American Pathologists (CAP) serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

We would like to thank NGS for the opportunity to review and comment on its proposal to provide coverage for targeted genomic sequence panels in the diagnosis of Myelodysplastic Syndromes (MDS). We agree with NGS's view that there is sufficient evidence to support testing for patients with signs or symptoms of MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) overlap syndromes in which other assessments are non-diagnostic. However, we recommend two specific additions to this policy that we believe are clinically appropriate:

1. Myelodysplastic syndromes can be difficult to diagnose. Several other benign or reactive diseases closely resemble these syndromes and can be confused with MDS, including, but not limited to, aplastic anemia, certain leukemias, HIV infection, an overactive immune system and other chronic medical diseases. Patients being evaluated for a possible MDS diagnosis typically have an otherwise unexplained cytopenia (with CBC's showing low leukocyte, platelet, and/or red cell counts). Proper and timely diagnosis is crucial to receiving the most-effective treatment for MDS. In addition, timely diagnosis of MDS will reduce so called "diagnostic odysseys" and likely prevent downstream wastage of important healthcare dollars. Current NCCN clinical practice guidelines for Myelodysplastic Syndromes specify that:

   Bone marrow or peripheral blood cells may be assayed for MDS-associated gene mutations. These can establish the presence of clonal hematopoiesis, which can help exclude benign causes of cytopenias in cases with non-diagnostic morphology.

Request: Please consider adding coverage for the following list of additional diagnosis codes for diseases and conditions other than MDS that have similar signs and symptoms (typically cytopenias of various hematopoietic cell lineages) that can often not be distinguished from MDS, even after a bone marrow

biopsy. In patients with these diagnoses, genomic sequencing is clinically useful to 'rule out' MDS so that the underlying non-malignant cause of the patient's cytopenias can be diagnosed and treated. This list is not intended to be comprehensive.

ICD-10	Description
D72.810	Lymphocytopenia
D72.818	Other decreased white blood cell count
D72.819	Decreased white blood cell count, unspecified
D61.818	Other pancytopenia
D69.6	Thrombocytopenia, unspecified
D70.9	Neutropenia, unspecified
D70.8	Other neutropenia
C94.6	Myelodysplastic disease, not classified

2. With regard to the draft LCD's global non-coverage for repeat genomic sequencing after the initial diagnosis of MDS, we are aware of some limited clinical scenarios whereby repeat testing is clinically indicated. For example, MDS often evolves into frank acute myeloid leukemia, and the spectrum of mutations in that later stage AML is often quite different than in the prior MDS. Repeat genomic sequencing in this instance may be helpful for both prognostic and therapeutic purposes in that it may change the prognostic outlook and/or necessitate a different therapeutic strategy that will reduce waste and maximize therapeutic efficacy.

   Several mutations in AML evolved from MDS are well documented to be a specific predictive biomarker for choosing an effective targeted therapy. Midostaurin treatment for FLT3-mutated AML and ATRA for AML with evidence of PML-RARA fusion are just two examples. IDH inhibitors are in the final stages of clinical development and have shown great promise in AMLs harboring IDH mutations. On August 1, 2017, Idhifa (enasidenib) received FDA approval for the treatment of adult patients with relapsed or refractory AML who have mutations in the IDH2 gene. Other AML mutations are proven prognostic biomarkers that assist in determining applicability of stem cell transplantation (ie, TP53, FLT3, NPM1, CEBPA). Many of these actionable alterations can be acquired during the course of time in patients with MDS who evolve into AML, such that a repeat mutation profile is clinically indicated to determine optimal management. The role of these predictive and prognostic mutations in choosing optimal therapy for AML patients is standard of care as defined by the current NCCN Clinical Practice Guidelines for Acute Myeloid Leukemia.

   It's also important to keep in mind that these genomic markers can help to identify when expensive therapy options such as transplant may be ineffective. For example, the cost for a transplant can exceed hundreds of thousands of healthcare dollars. Certain alterations such as TP53 mutation can identify patients who are unlikely to benefit from transplant.

   Therefore, from both a patient care and economic perspective, it is sometimes clinically appropriate to molecularly monitor patients with MDS at more than just one time point. Furthermore, NGS' Local Coverage Determination for Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926) does not preclude repeat testing.

Request: We request that the LCD include language allowing for repeat genomic testing where clinically indicated and appropriate.

Thank you again for the opportunity to review and comment on this proposed policy. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Director of Public Policy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists