November 6, 2020

Gabriel A. Bien-Willner, M.D., Ph.D.
Medical Director
MolDX at Palmetto GBA

RE: Proposed Local Coverage Determination (LCD): Minimal Residual Disease Testing for Cancer (DL38779)

Dear Dr. Bien-Willner,

The American Society of Hematology (ASH) is pleased to offer comments on the proposed local coverage determination (LCD), Minimal Residual Disease (MRD) Testing for Cancer (DL38779).

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

Specifically, ASH is commenting on the following:

1. First criterion related to Next Generation Sequencing National Coverage Determination
2. Terminology
   a. Minimum versus minimal
   b. Protease inhibitors versus proteasome inhibitors
3. Inclusion of Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML)

First Criterion Related to Next Generation Sequencing National Coverage Determination

The first criterion in the LCD limits coverage to only those patients that have “not been previously tested with the same test for the same genetic content.” ASH disagrees and asks for the elimination of this first criterion for MRD testing for blood cancers. The Society believes this language to be confusing and inaccurate. When testing for MRD in a patient with a hematologic malignancy, the treating physician is frequently assessing whether a pre-treatment marker of disease has decreased or disappeared completely. As such, conventional MRD assessment at the end of treatment necessitates that a baseline (or pre-treatment) test already be completed. Moreover, additional assessments of MRD may be required for (1) longitudinal monitoring or surveillance (for example, in patients with Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), or Chronic Myeloid Leukemia (CML)), (2) to again assess for end of treatment responses in patients receiving multiple/additional lines of therapy, and (3) to determine response prior to
allogeneic stem cell transplantation. ASH refers you to the National Comprehensive Cancer Network (NCCN) guidelines for AML and ALL, which support repeated measures of MRD.¹,²

**Terminology**

*Minimum versus minimal*

In the background section of the LCD, the language refers to “minimum” residual disease. ASH recommends use of the word “minimal” rather than “minimum” as it is more commonly used in the literature and by clinical experts. Additionally, the Society requests the addition of the word “measurable” when describing MRD in the background section. The term “minimal” can be misleading, as even the low-level disease detected may be significant in terms of prognosis and treatment decision-making. The term “measurable” more accurately describes the presence of the cancer cells remaining in a patient.³ The NCCN guidelines use both terms, “minimal” and “measurable.”¹,⁴

*Protease Inhibitors Versus Proteasome Inhibitors*

In the multiple myeloma (MM) section of the LCD, ASH recommends deleting the term “protease inhibitors” and replacing it with the term “proteasome inhibitors.” Protease inhibitors are a different drug class from proteasome inhibitors. The former are the anti-viral therapies used in HIV infection. The latter are inhibitors of the proteasome, which is a key protein structure in myeloma.

**Inclusion of Acute Myeloid Leukemia (AML) and Chronic Myeloid Leukemia (CML)**

The draft LCD states that MRD use in certain hematological malignancies has been well established in the scientific literature and is used as a patient risk stratification tool and to guide treatment decisions. Specifically, the LCD names ALL, MM, and chronic lymphocytic leukemia (CLL). ASH urges the addition of AML and CML to this list of hematologic malignancies. For AML, the goal for all patients should be to achieve a complete remission without MRD after chemotherapy. MRD testing for AML is prognostically important, since survival and relapse-free survival are significantly lower in patients with MRD.³ In addition, MRD testing can help to determine if a patient should be referred for allogeneic hematopoietic cell transplantation (HCT) to increase the chance of curing the underlying AML.⁶ In CML, molecular testing primarily consists of longitudinal polymerase chain reaction (PCR)-based monitoring; well-established targets for molecular testing changes over time guide therapeutic decision-making, including the need to switch therapies or refer for allogeneic HCT.

Thank you for the opportunity to provide comments on the proposed LCD, Minimal Residual Disease Testing for Cancer. This is an extremely important tool in the treatment of patients with hematologic cancers and we appreciate the thoughtful approach taken in the LCD. We welcome the opportunity to discuss these comments with you and your team. If you have any questions or require further clarification, please contact Leslie Brady, ASH Policy and Practice Manager at lbrady@hematology.org or 716-361-2764.

Sincerely,

Stephanie J. Lee, MD, MPH
President