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RE: MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (DL38047)

Dear Dr. Bien-Willner:

On behalf of the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), we thank you for the opportunity to review and comment on Palmetto GBA's proposed coverage policy for MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (DL38047).

AMP is an international medical and professional association representing approximately 2,500 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 academic medicine, hospital-based and private clinical laboratories, the government 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 CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

We are submitting joint comments because at this time both of our organizations share the same perspective regarding this draft LCD. We appreciate the effort that has gone into the development of this proposed LCD, and we offer the following recommendations for Palmetto's consideration.

Proposed Coverage Policy

AMP and CAP applaud Palmetto's efforts to clarify coverage for next-generation sequencing (NGS) lab-developed tests (LDTs) for myeloid malignancies and suspected myeloid malignancies. We hope this policy will ensure patients with cytopenias and cytoses, as well as diagnosed myelodysplastic syndrome (MDS), myeloproliferative

neoplasms (MPN), overlap myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukemia (AML) will have access to medically necessary testing.

The proposed LCD references more than 70 genes that have been identified as having clinical utility in acute and chronic myeloid disorders. AMP and CAP believe that there are at least 65 genes that, when mutated, are clinically informative for therapeutic decision making, e.g. diagnosis, risk stratification for hematopoietic stem cell transplant, and/or targeted therapy) – as listed in the attached table 1. Based on this detailed list of clinically relevant gene mutations for myeloid malignancies, we recommend that Palmetto expand coverage for NGS-based testing to include panels with 51 or more genes, consistent with CPT code 81455. (Mukherjee et al., 2017). This specific CPT code change is included later in this letter.

Recommendations Regarding Criteria for Coverage

- I. The policy provides the following coverage criteria:

The assay performed includes at least the minimum genes and positions indicated for its intended use, as described in an associated coverage Article and found in the technical assessment (TA) forms.

AMP and CAP applaud the transparency associated with connecting DL38047 to a specific list of biomarkers, described in Form #M00154. This content is of enormous importance to MoDx, to those who design and validate such tests, and to the beneficiaries impacted by their results. We suggest the following to ensure this list achieves its goals:

1. Please clarify the scientific evidence for the selected “required variant coverage” biomarkers (variants in 26 genes) listed in Form #M00154.
 - a. Some of the specific loci listed are of unclear clinical significance to AMP and CAP experts and should not be required for panels to be reimbursed.
 - b. For those genes with documented myeloid cell pathogenicity due to loss of protein function (i.e., tumor suppressor genes such as ASXL1, RUNX1, and TET2), it has been shown that any loss of function mutation, and not just mutations at “hotspots”, can contribute to disease pathogenicity (Sperling et al., 2017).
2. AMP and CAP suggest the creation of a workgroup of experts whose sole objective would be to finalize a gene/variant list that satisfies the MoDx “at least” criteria.
 - a. 2-3 meetings would suffice to compile this gene/variant, and a July 2019 completion date would be feasible
 - b. A sample gene list is attached to this letter (Table 1 – FINAL)

- II. The policy provides the following coverage criteria:

Testing is performed on bone marrow biopsies or peripheral blood samples.

AMP and CAP are supportive of Palmetto’s proposal to cover testing performed on bone marrow biopsies or peripheral blood samples. However, we recommend that these criteria be revised to also allow for biopsies of hematopoietic tissues located outside of bone marrow and peripheral blood. Bone marrow aspirate or bone marrow clot is a more common sample type than bone marrow biopsies that can be utilized for next generation sequencing analysis. We also recommend that specimen type be expanded to include extramedullary tissue biopsies, since myeloid malignancies (i.e., myeloid sarcoma) not uncommonly present at extramedullary sites. The ICD-10 code for myeloid sarcoma is an accepted diagnosis code, so it is important that testing can be performed

for these patients on involved tissue. Although uncommon, acute myeloid leukemia can present in the skin (as cutaneous myeloid sarcoma, or leukemia cutis) or other solid organs prior to peripheral blood or bone marrow involvement (Moyer et al., 2018).

Therefore, we recommend revising the proposed coverage statement to read:

Testing is performed on an appropriate biopsy specimen such as extramedullary tissue biopsies, bone marrow biopsies, bone marrow aspirate or clot, or peripheral blood samples.

III. The policy includes the following regarding repeat testing:

For patients that do not have a diagnosis of a myeloid malignancy, where one is suspected, the patient must have an undefined cytopenia for greater than 6 months, other possible causes have been reasonably excluded.

The proposed policy states that NGS detection of clonal hematopoiesis with mutation detection in patients with an unexplained cytopenia of greater than 4 months is a strong predictor of who has or will have a myeloid disorder. AMP and CAP are concerned that the coverage criteria specifies that initial testing is only covered after more than 6 months for an undefined cytopenia, and we recommend that Palmetto revise this criterion to allow more frequent testing for the evaluation of clinically-relevant clonal evolution. Results of residual disease testing are also used to make adjustments to the level of immunosuppressive agents after transplant, or to alter levels of post-transplant targeted therapy to maximize response while minimizing adverse side effects.

In addition, the National Comprehensive Cancer Network (NCCN) guidelines and key new literature state that, for AML and MDS, repeat testing is appropriate after one month (and before stem cell transplantation) for prognostically-relevant minimal residual disease (MRD) detection. We recommend that the coverage policy should reflect these repeat testing guidelines (Acute myeloid leukemia NCCN Guidelines, 2019; Jongen-Lavrencic et al., 2018). Furthermore, allogeneic hematopoietic stem-cell transplantation is the only curative treatment for patients with myelodysplastic syndrome (MDS). However, disease progression after transplantation remains a problem in patients with MDS. NGS to monitor the detection of tumor cells and MRD at pre-relapse time points, such as 30 days after transplantation, has the potential to improve outcomes for patients with myeloid malignancies (Duncavage et al., 2018). Therefore, repeat testing for the evaluation of MRD in both AML and MDS is clinically relevant.

Recommendations Regarding Situations in which a Test Should Not Be Used or Coverage is Denied

IV. The policy provides for non-coverage in cases where no TA has been completed:

A Technical Assessment has not been satisfactorily completed by MOLDX. For tests that are currently covered but a TA submission has not been made, providers must submit complete TA materials by October 1st, 2019 or coverage will be denied.

We understand that a test must successfully undergo a TA by MolDx in order to be eligible for coverage. However, we believe that there is a need for increased transparency regarding how responses in the TA document may impact coverage determinations. For example, the TA for myeloid panels, Form #M00154, is onerous and difficult to understand.

Many of the indicated variant positions listed on this form are not frequently mutated in myeloid malignancies, and others are not the correct amino acid at the indicated position using preferred reference sequences. As mentioned previously in this letter, clarification is necessary regarding whether the listed genes represent a “minimum required list.” We note that some key genes in myeloid neoplasia are not included, and one listed gene, *STAT3*, is primarily implicated in lymphoid rather than myeloid malignancies and would not be included in many hot spot myeloid panels, despite its utility in the work-up of non-myeloid causes of neutropenia.

In addition, a “minimum required list” is likely to be a moving target since new FDA-approvals for therapies targeting mutations in myeloid malignancies (e.g., gene fusion) are likely to be forthcoming. Given the complexity of an NGS validation study, laboratories and manufacturers will need a reasonable time period to develop and validate expanded panels before MoDx changes coverage eligibility. It is also possible that a laboratory may need to supplement an NGS assay with a single gene assay (e.g., gene fusion). When and if this occurs, we encourage MoDx to work with providers to ensure that an update to the required list does not result in non-coverage and reduced patient access to these procedures.

- V. Above, we documented the clinical and scientific rationale for our recommendation to allow repeat NGS-based testing. We also want to express our concerns about the following language included in the non-coverage section:

Another NGS test was performed for the same indication within the past 6 months.

There is convincing evidence in the literature that 6 months is too long of a time interval to have to wait for a repeat NGS-based test. In AML patients, the detection of post-treatment MRD has thus been shown to be an excellent prognosticator of future relapse at various post-treatment time points including after induction chemotherapy, (day 30) (Jongen 2018; Rothenberg 2018; NCCN guidelines) before stem cell transplantation (Press 2019; Thol 2018; NCCN guidelines), and after stem cell transplantation (Kim 2018).

Given that these well-documented clinically-relevant MRD assessment time points typically all occur within a few months of the initial AML diagnosis, we urge Palmetto to not automatically reject repeat NGS-based testing within 6 months of the prior NGS test, but instead consider covering repeat MRD testing more frequently than every 6 months in the appropriate clinical context.

CPT Coding

We recommend the inclusion of additional CPT codes for targeted genomic sequencing. The additional codes include, but may not be limited to, those listed below:

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

ICD-10 Coding

We request that additional ICD-10 codes be added to the local coverage article A54795 including, but not be limited to the following list:

C88.8 Other malignant immunoproliferative diseases
 C92 Myeloid leukemia
 C92.0 Acute myeloblastic leukemia
 C92.01 Acute myeloblastic leukemia, in remission
 C92.1 Chronic myeloid leukemia, BCR/ABL-positive
 C92.2 Atypical chronic myeloid leukemia, BCR/ABL-negative
 C92.3 Myeloid sarcoma
 C92.31 Myeloid sarcoma, in remission
 C92.4 Acute promyelocytic leukemia
 C92.41 Acute promyelocytic leukemia, in remission
 C92.5 Acute myelomonocytic leukemia
 C92.51 Acute myelomonocytic leukemia, in remission
 C92.6 Acute myeloid leukemia with 11q23-abnormality
 C92.61 Acute myeloid leukemia with 11q23-abnormality, in remission
 C92.90 Myeloid leukemia, unspecified, not having achieved remission
 C92.92 Myeloid leukemia, unspecified in relapse
 C92.A Acute myeloid leukemia with multilineage dysplasia
 C92.A1 Acute myeloid leukemia with multilineage dysplasia, in remission
 C92.Z Other myeloid leukemia
 C92.Z1 Other myeloid leukemia, in remission
 C92.9 Myeloid leukemia, unspecified
 C92.90 Myeloid leukemia, unspecified, not having achieved remission
 C92.91 Myeloid leukemia, unspecified in remission
 C92.92 Myeloid leukemia, unspecified in relapse
 C93.00 Acute monoblastic/monocytic leukemia, not having achieved remission
 C93.01 Acute monoblastic/monocytic leukemia, in remission
 C93.02 Acute monoblastic/monocytic leukemia, in relapse
 C93.12 Chronic myelomonocytic leukemia, in relapse
 C93.Z0 Other monocytic leukemia, not having achieved remission
 C93.Z2 Other monocytic leukemia, in relapse
 C93.90 Monocytic leukemia, unspecified, not having achieved remission
 C93.92 Monocytic leukemia, unspecified in relapse
 C94.01 Acute erythroid leukemia, in remission
 C94.21 Acute megakaryoblastic leukemia, in remission
 C94.8 Other specified leukemias
 C94.80 Other specified leukemias not having achieved remission
 C94.81 Other specified leukemias, in remission
 C94.82 Other specified leukemias, in relapse
 C95.00 Acute leukemia of unspecified cell type not having achieved remission
 C95.02 Acute leukemia of unspecified cell type, in relapse
 C95.10 Chronic leukemia of unspecified cell type not having achieved remission
 C95.12 Chronic leukemia of unspecified cell type, in relapse
 C95.90 Leukemia, unspecified not having achieved remission
 C95.92 Leukemia, unspecified, in relapse
 C96.2 Malignant mast cell tumor
 C96.9 Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified

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| C96.Z | Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue |
| D47 | Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue |
| D47.2 | Monoclonal gammopathy |
| D47.Z | Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue |
| D47.Z1 | Post-transplant lymphoproliferative disorder (PTLD) |
| D59.1 | Other autoimmune hemolytic anemias |
| D59.4 | Other nonautoimmune hemolytic anemias |
| D59.8 | Other acquired hemolytic anemias |
| D59.9 | Acquired hemolytic anemia, unspecified |
| D61.09 | Other constitutional aplastic anemia |
| D61.3 | Idiopathic aplastic anemia |
| D61.818 | Other pancytopenia |
| D61.9 | Aplastic anemia, unspecified |
| D61.818 | Other pancytopenia |
| D61.8/ D61.89 | Other specified aplastic anemias and other bone marrow failure syndromes |
| D61.9 | Aplastic anemia, unspecified |
| D64.9 | Anemia, unspecified |
| D69.49 | Other primary thrombocytopenia |
| D69.6 | Thrombocytopenia, unspecified |
| D69.8 | Other specified hemorrhagic conditions |
| D69.9 | Hemorrhagic condition, unspecified |
| D69.3 | Immune thrombocytopenic purpura |
| D69.49 | Other primary thrombocytopenia |
| D69.59 | Other secondary thrombocytopenia |
| D69.6 | Thrombocytopenia, unspecified |
| D70.4 | Cyclic neutropenia |
| D70.8 | Other neutropenia |
| D70.9 | Neutropenia, unspecified |
| D72 | Other disorders of white blood cells |
| D72.0 | Genetic anomalies of leukocytes |
| D72.1 | Eosinophilia |
| D72.8 | Other specified disorders of white blood cells |
| D72.81 | Decreased white blood cell count |
| D72.810 | Lymphocytopenia |
| D72.818 | Other decreased white blood cell count |
| D72.819 | Decreased white blood cell count, unspecified |
| D72.82 | Elevated white blood cell count |
| D72.818 | Other decreased white blood cell count |
| D72.819 | Decreased white blood cell count, unspecified |
| D72.820 | Lymphocytosis (symptomatic) |
| D72.828 | Other elevated white blood cell count |
| D72.829 | Elevated white blood cell count, unspecified |
| D72.89 | Other specified disorders of white blood cells |
| D72.9 | Disorder of white blood cells, unspecified |
| D75 | Other and unspecified diseases of blood and blood-forming organs |
| D75.8 | Other specified diseases of blood and blood-forming organs |

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| D77 | Other disorders of blood and blood-forming organs in diseases classified elsewhere |
| J82 | Pulmonary eosinophilia, not elsewhere classified |
| Q82.2 | Mastocytosis |
| R16.1 | Splenomegaly, not elsewhere classified |
| R16.2 | Hepatomegaly with splenomegaly, not elsewhere classified |

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 Senior 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

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