



November 7, 2020

CGS Administrators, LLC  
Meredith Loveless, MD  
Attn: Medical Review  
26 Century Blvd., Ste ST610  
Nashville, TN 37214-3685

Palmetto GBA  
Part B Policy  
PO Box 100238 (JM) and  
PO Box 100305 (JJ)  
AG-275 Columbia, SC 29202

Noridian Healthcare Solutions, LLC  
Part B Contractor Medical Director(s)  
Attention: Draft LCD Comments  
PO Box 6781  
Fargo, ND 58108-6781

Wisconsin Physicians Service  
Ella Noel, D.O., FACOI  
1717 West Broadway  
Madison, WI 53713

Re: MoIDX: Minimal Residual Disease Testing for Cancer  
CGS Administrators DL38822  
Noridian (JE) DL38814 and (JF) DL38816  
Palmetto (JJ) and (JM) DL38779  
Wisconsin Physicians Service (J5) and (J8) DL38835

Dear Medical Directors:

The Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) write to provide joint comments on MoIDX's proposed coverage policy for Minimal Residual Disease Testing for Cancer. We appreciate the opportunity to review and provide joint comments as our organizations share the same perspective regarding this draft LCD.

The 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 the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

The CAP is the world's largest organization of board-certified pathologists and the leading provider of laboratory accreditation and proficiency testing programs. The CAP serves patients, physicians, hospitals and healthcare systems worldwide, fostering and advocating excellence in the practice of pathology and laboratory medicine.

Together, we would like to thank you for proposing coverage of minimal residual disease testing (MRD) for cancer. We believe thoughtful consideration was given to this issue, and the resulting proposed LCD will positively impact patient care and other payers will be encouraged to follow with other less expensive testing for cancer. Further, we appreciate the addition of the following language about future revisions to the LCD as technology evolves:

*This remains a rapidly evolving field, and we anticipate that new evidence may emerge either showing limitations of the clinical utility underlying MRD testing or additional strengths and new applications. Additionally, this coverage decision is based heavily on paradigm for care which was not developed for MRD testing. In summary, we anticipate future revisions to this coverage decision as the science and standard of care evolves, which may further limit or expand coverage for MRD testing.*

AMP and CAP fully agree that this is a necessary addition to the proposed coverage policy.

Below and outlined in this comment letter are AMP and CAP's recommendations for the draft LCD and we appreciate your consideration of our comments.

### **Coverage Indications, Limitations, and/or Medical Necessity**

AMP and CAP wish to provide the following comments on specific coverage requirements included in the draft LCD:

1. *If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD90.2 are fulfilled (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously tested with the same test for the same genetic content) or are not applicable (the patient does not have cancer as defined below)*

MRD testing has two very important uses—to diagnose cancer recurrence before clinical or radiological evidence, and to monitor response to therapy. Monitoring response to therapy automatically involves testing more than once during the lifetime of a patient as it is repeated over the duration of the treatment. It is important to note that an initial diagnostic test may or may not be the same assay that is utilized to follow a patient over time, depending on the design of the test panel. If you are using the same NGS-based test for diagnosis and monitoring, there will be more than one of these tests performed during the patient's lifetime.

AMP and CAP recognize that this proposed LCD needs to be designed within the parameters set forth in NCD90.2, which provides contractors authority to cover NGS tests as a diagnostic laboratory test for patients with cancer in certain circumstances, and includes language which appears to place certain restrictions on repeat testing. AMP and CAP interpret the NCD language as serving to block duplicative NGS testing, while, at the same time allowing repeat testing for different and evolving genetic content (i.e., testing that is performed to monitor response to therapy). Thus, MRD testing using NGS-based methods for the use of monitoring a patient's response to therapy is outside the scope of the NCD (i.e., monitoring is not a diagnostic test). **Our organizations recommend adding language to the LCD making this distinction clear to eliminate any confusion.** AMP and CAP offer to be a resource for further discussions on the flexibility of testing.

As drafted, the policy states the following:

*MRD testing often requires two types of assays to be performed as part of the service. First, a sample is taken from tumor diagnostic material to establish a baseline tumor signature as defined by the test methodology. This is followed by a series assays run on blood to detect the presence or recurrence of tumor based on the measured biomarkers, expression, or other analytes over various timepoints. This series of assays comprises a single test when the patient is known to have cancer.*

MolDX has designed an LCD that appears to allow for MRD testing by applying and then circumventing the repeat testing provision within NCD 90.2 by encompassing a series of assays as one service. **AMP and CAP seek clarity on exactly how such processes will be set forth in clinical practice. We request that MolDX provide greater transparency about what the protocol is for the process of monitoring a disease state over time using**

**MRD testing at the local coverage level (e.g., how ordering and billing are performed if “a series of assays comprises a single test” as described in the LCD).**

We are concerned that this criterion will create a significant administrative burden for laboratories and is not necessary if the repeat testing provision within the NCD is appropriately applied to only repeat diagnostic testing using the same genetic content.

**Furthermore, we request clarification on whether this LCD only applies to NGS-based testing or if it will also cover a single gene assays used for monitoring.** As previously mentioned, there are different indications for testing – diagnosis and monitoring over time as with MRD. For example, in AML there is monitoring via key translocations [t(15;17), t(8;21), inv(16), and t(9;22)] as well as individual expression levels or mutations in WT1, NPM1, FLT3-ITD, RUNX1. Additionally, for AML it is well established to do single gene MRD for NPM1 mutations by qPCR (Ivey A et al, 2016; Dillon R et al, 2020; Kapp-Schworer S et al, 2020; Thol F et al, 2018). This field is and will continue to evolve rapidly and some tests may be practical to use every month or every other month as opposed to on a quarterly or one-time basis, and other tests might be more adequate to use just once to guide adjunctive therapy decisions.

5. *The test is demonstrated to identify recurrence or progression with sensitivity and specificity that is considerably more accurate than other established (non-MRD) forms of surveillance or monitoring. To be reasonable and necessary, it must also be medically acceptable that the test being utilized precludes other surveillance or monitoring tests unless they are required to follow-up or confirm the findings of this test*

**AMP and CAP request that MoIDX define “medically acceptable” and/or provide clarification on who might determine whether something is considered “medically acceptable.”**

#### **MRD in Hematopoietic Malignancies**

We recognize and appreciate that MoIDX specifically mentions the following three disease states that are specifically mentioned in the National Comprehensive Cancer Network (NCCN) guidelines: acute lymphoblastic leukemia (ALL), Multiple Myeloma (MM), and Chronic Lymphocytic Leukemia (CLL). **However, we request that MoIDX consider including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) to the list of disease states.** Molecular MRD testing for AML and MDS has been shown in multiple studies to be a strong and early predictor of relapse risk for patients treated with both conventional chemotherapy and stem cell transplant. The references listed in this letter below include research and evidence that demonstrates clinical utility of molecular MRD in AML and MDS in panel based NGS, single gene mutation assays, and translocation-based qPCR. Again, as uses for MRD testing grows, we offer AMP and CAP member expertise as a resource to MoIDX to help ensure this LCD aligns with current evidence.

#### **ICD-10 Coding**

**We request additional ICD-10 codes be added to the associated coverage article including, but not be limited to, the following:**

C61	Malignant neoplasm of prostate
C82	Follicular lymphoma
C82.0	Follicular lymphoma grade I
C82.00	Follicular lymphoma grade I, unspecified site
C82.01	Follicular lymphoma grade I, lymph nodes of head, face, and neck
C82.02	Follicular lymphoma grade I, intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I, intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I, lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I, lymph nodes of inguinal region and lower limb

C82.06 Follicular lymphoma grade I, intrapelvic lymph nodes  
 C82.07 Follicular lymphoma grade I, spleen  
 C82.08 Follicular lymphoma grade I, lymph nodes of multiple sites  
 C82.09 Follicular lymphoma grade I, extranodal and solid organ sites  
 C82.1 Follicular lymphoma grade II  
 C82.10 Follicular lymphoma grade II, unspecified site  
 C82.11 Follicular lymphoma grade II, lymph nodes of head, face, and neck  
 C82.12 Follicular lymphoma grade II, intrathoracic lymph nodes  
 C82.13 Follicular lymphoma grade II, intra-abdominal lymph nodes  
 C82.14 Follicular lymphoma grade II, lymph nodes of axilla and upper limb  
 C82.15 Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb  
 C82.16 Follicular lymphoma grade II, intrapelvic lymph nodes  
 C82.17 Follicular lymphoma grade II, spleen  
 C82.18 Follicular lymphoma grade II, lymph nodes of multiple sites  
 C82.19 Follicular lymphoma grade II, extranodal and solid organ sites  
 C82.2 Follicular lymphoma grade III, unspecified  
 C82.20 Follicular lymphoma grade III, unspecified, unspecified site  
 C82.21 Follicular lymphoma grade III, unspecified, lymph nodes of head, face, and neck  
 C82.22 Follicular lymphoma grade III, unspecified, intrathoracic lymph nodes  
 C82.23 Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes  
 C82.24 Follicular lymphoma grade III, unspecified, lymph nodes of axilla and upper limb  
 C82.25 Follicular lymphoma grade III, unspecified, lymph nodes of inguinal region and lower limb  
 C82.26 Follicular lymphoma grade III, unspecified, intrapelvic lymph nodes  
 C82.27 Follicular lymphoma grade III, unspecified, spleen  
 C82.28 Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites  
 C82.29 Follicular lymphoma grade III, unspecified, extranodal and solid organ sites  
 C82.3 Follicular lymphoma grade IIIa  
 C82.30 Follicular lymphoma grade IIIa, unspecified site  
 C82.31 Follicular lymphoma grade IIIa, lymph nodes of head, face, and neck  
 C82.32 Follicular lymphoma grade IIIa, intrathoracic lymph nodes  
 C82.33 Follicular lymphoma grade IIIa, intra-abdominal lymph nodes  
 C82.34 Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb  
 C82.35 Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb  
 C82.36 Follicular lymphoma grade IIIa, intrapelvic lymph nodes  
 C82.37 Follicular lymphoma grade IIIa, spleen  
 C82.38 Follicular lymphoma grade IIIa, lymph nodes of multiple sites  
 C82.39 Follicular lymphoma grade IIIa, extranodal and solid organ sites  
 C82.4 Follicular lymphoma grade IIIb  
 C82.40 Follicular lymphoma grade IIIb, unspecified site  
 C82.41 Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck  
 C82.42 Follicular lymphoma grade IIIb, intrathoracic lymph nodes  
 C82.43 Follicular lymphoma grade IIIb, intra-abdominal lymph nodes  
 C82.44 Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb  
 C82.45 Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb  
 C82.46 Follicular lymphoma grade IIIb, intrapelvic lymph nodes  
 C82.47 Follicular lymphoma grade IIIb, spleen  
 C82.48 Follicular lymphoma grade IIIb, lymph nodes of multiple sites  
 C82.49 Follicular lymphoma grade IIIb, extranodal and solid organ sites  
 C82.5 Diffuse follicle center lymphoma  
 C82.50 Diffuse follicle center lymphoma, unspecified site

C82.51 Diffuse follicle center lymphoma, lymph nodes of head, face, and neck  
 C82.52 Diffuse follicle center lymphoma, intrathoracic lymph nodes  
 C82.53 Diffuse follicle center lymphoma, intra-abdominal lymph nodes  
 C82.54 Diffuse follicle center lymphoma, lymph nodes of axilla and upper limb  
 C82.55 Diffuse follicle center lymphoma, lymph nodes of inguinal region and lower limb  
 C82.56 Diffuse follicle center lymphoma, intrapelvic lymph nodes  
 C82.57 Diffuse follicle center lymphoma, spleen  
 C82.58 Diffuse follicle center lymphoma, lymph nodes of multiple sites  
 C82.59 Diffuse follicle center lymphoma, extranodal and solid organ sites  
 C82.8 Other types of follicular lymphoma  
 C82.80 Other types of follicular lymphoma, unspecified site  
 C82.81 Other types of follicular lymphoma, lymph nodes of head, face, and neck  
 C82.82 Other types of follicular lymphoma, intrathoracic lymph nodes  
 C82.83 Other types of follicular lymphoma, intra-abdominal lymph nodes  
 C82.84 Other types of follicular lymphoma, lymph nodes of axilla and upper limb  
 C82.85 Other types of follicular lymphoma, lymph nodes of inguinal region and lower limb  
 C82.86 Other types of follicular lymphoma, intrapelvic lymph nodes  
 C82.87 Other types of follicular lymphoma, spleen  
 C82.88 Other types of follicular lymphoma, lymph nodes of multiple sites  
 C82.89 Other types of follicular lymphoma, extranodal and solid organ sites  
 C82.9 Follicular lymphoma, unspecified  
 C82.90 Follicular lymphoma, unspecified, unspecified site  
 C82.91 Follicular lymphoma, unspecified, lymph nodes of head, face, and neck  
 C82.92 Follicular lymphoma, unspecified, intrathoracic lymph nodes  
 C82.93 Follicular lymphoma, unspecified, intra-abdominal lymph nodes  
 C82.94 Follicular lymphoma, unspecified, lymph nodes of axilla and upper limb  
 C82.95 Follicular lymphoma, unspecified, lymph nodes of inguinal region and lower limb  
 C82.96 Follicular lymphoma, unspecified, intrapelvic lymph nodes  
 C82.97 Follicular lymphoma, unspecified, spleen  
 C82.98 Follicular lymphoma, unspecified, lymph nodes of multiple sites  
 C82.99 Follicular lymphoma, unspecified, extranodal and solid organ sites  
 C92 Myeloid leukemia  
 C92.0 Acute myeloblastic leukemia  
 C92.00 Acute myeloblastic leukemia, not having achieved remission  
 C92.01 Acute myeloblastic leukemia, in remission  
 C92.02 Acute myeloblastic leukemia, in relapse  
 C92.3 Myeloid sarcoma  
 C92.30 Myeloid sarcoma, not having achieved remission  
 C92.31 Myeloid sarcoma, in remission  
 C92.32 Myeloid sarcoma, in relapse  
 C92.4 Acute promyelocytic leukemia  
 C92.40 Acute promyelocytic leukemia, not having achieved remission  
 C92.41 Acute promyelocytic leukemia, in remission  
 C92.42 Acute promyelocytic leukemia, in relapse  
 C92.5 Acute myelomonocytic leukemia  
 C92.50 Acute myelomonocytic leukemia, not having achieved remission  
 C92.51 Acute myelomonocytic leukemia, in remission  
 C92.52 Acute myelomonocytic leukemia, in relapse  
 C92.6 Acute myeloid leukemia with 11q23-abnormality  
 C92.60 Acute myeloid leukemia with 11q23-abnormality not having achieved remission

C92.61 Acute myeloid leukemia with 11q23-abnormality in remission  
 C92.62 Acute myeloid leukemia with 11q23-abnormality in relapse  
 C92.A Acute myeloid leukemia with multilineage dysplasia  
 C92.A0 Acute myeloid leukemia with multilineage dysplasia, not having achieved remission  
 C92.A1 Acute myeloid leukemia with multilineage dysplasia, in remission  
 C92.A2 Acute myeloid leukemia with multilineage dysplasia, in relapse  
 C92.Z Other myeloid leukemia  
 C92.Z0 Other myeloid leukemia not having achieved remission  
 C92.Z1 Other myeloid leukemia, in remission  
 C92.Z2 Other myeloid leukemia, in relapse  
 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  
 C94 Other leukemias of specified cell type  
 C94.0 Acute erythroid leukemia  
 C94.00 Acute erythroid leukemia, not having achieved remission  
 C94.01 Acute erythroid leukemia, in remission  
 C94.02 Acute erythroid leukemia, in relapse  
 C94.2 Acute megakaryoblastic leukemia  
 C94.20 Acute megakaryoblastic leukemia not having achieved remission  
 C94.21 Acute megakaryoblastic leukemia, in remission  
 C94.22 Acute megakaryoblastic leukemia, in relapse  
 C94.3 Mast cell leukemia  
 C94.30 Mast cell leukemia not having achieved remission  
 C94.31 Mast cell leukemia, in remission  
 C94.32 Mast cell leukemia, in relapse  
 C94.4 Acute panmyelosis with myelofibrosis  
 C94.40 Acute panmyelosis with myelofibrosis not having achieved remission  
 C94.41 Acute panmyelosis with myelofibrosis, in remission  
 C94.42 Acute panmyelosis with myelofibrosis, in relapse  
 C94.6 Myelodysplastic disease, not classified  
 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  
 D46 Myelodysplastic syndromes  
 D46.0 Refractory anemia without ring sideroblasts, so stated  
 D46.1 Refractory anemia with ring sideroblasts  
 D46.2 Refractory anemia with excess of blasts [RAEB]  
 D46.20 Refractory anemia with excess of blasts, unspecified  
 D46.21 Refractory anemia with excess of blasts 1  
 D46.22 Refractory anemia with excess of blasts 2  
 D46.A Refractory cytopenia with multilineage dysplasia  
 D46.B Refractory cytopenia with multilineage dysplasia and ring sideroblasts  
 D46.C Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality  
 D46.4 Refractory anemia, unspecified  
 D46.Z Other myelodysplastic syndromes  
 D46.9 Myelodysplastic syndrome, unspecified

Thank you for the opportunity to provide comments on the proposed coverage policy for Minimal Residual Disease Testing for Cancer. Should you have any questions or require additional information, please direct your correspondence to Tara Burke, Senior Director of Public Policy and Advocacy, at [tburke@amp.org](mailto:tburke@amp.org) or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at [nwilson@cap.org](mailto:nwilson@cap.org).

Sincerely,

Association for Molecular Pathology  
College of American Pathology

### **References**

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