April 11, 2018

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LCD Comments
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RE: Molecular Pathology Procedures

Dear Ms. Muir,

Thank you for the opportunity to review and comment on National Government Services' proposed coverage policy for Molecular Pathology Procedures (DL35000). The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,400 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.

Members of both AMP and CAP are experts in molecular pathology and the implementation of this coverage policy will directly impact their practices. We are submitting joint comments because at this time both of our organizations share the same concerns regarding this draft LCD.

CPT codes 81120 (IDH1), 81121 (IDH2), 81175 and 81176 (ASXL1), 81334 (RUNX1), 81335 (TPMT), 81479 (MYD88)

With regard to these six new CPT category one codes: 81121, 81120, 81175, 81176, 81334, and 81335, and the new MYD88 indication for 81479 we request that NGS consider adding the following statements to the Coverage Guidance (Coverage Indications, Limitations, and/or Medical Necessity) and some additional ICD10 diagnosis codes that Support Medical Necessity to the final policy.

CPT Code 81120 (IDH1) and 81121 (IDH2)
IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C) is considered medically necessary in patients in patients with acute myeloid leukemia (AML), myeloproliferative neoplasms (MPN), and central nervous system gliomas to guide therapeutic decision making.

IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M) is considered medically necessary in patients in patients with acute myeloid leukemia (AML), myeloproliferative neoplasms (MPN) and central nervous system gliomas to guide therapeutic decision making.

Evidence:
MPN: IDH1/2 mutations are an independent predictor of poor prognosis in MPN acting as an essential factor in the decision whether a patient should undergo bone marrow transplant (2018 v2 NCCN myeloproliferative neoplasm guidelines).

AML: IDH2 mutations identify patients for treatment with enasidenib, a potent inhibitor of mutant IDH2 that promotes differentiation of myeloid cells in patients with advanced hematologic malignancies (2018 v1 NCCN AML guidelines, see page AML-12).

Glioma: NCCN central nervous system guidelines make the recommendation: IDH mutation testing is required for the workup of glioma (2018 v1 NCCN central nervous system cancer guidelines, see BRAIN-F (7 of 9)). "IDH mutations define WHO grade II and III astrocytomas and oligodendrogliomas, and the secondary grade IV glioblastomas into which astrocytomas often evolve. Their presence distinguishes lower-grade gliomas from primary glioblastomas, which are IDH wild type. Detection of these mutations in a specimen that is otherwise equivocal for tumor may also be regarded as evidence that diffusely infiltrative glioma is present"

Group 33 ICD-10 Codes Paragraph (IDH1/2)

The proposed policy lists the 3 ICD-10 codes for MPN. We agree that an exact diagnosis and ICD-10 should be known for a patient previously classified as having MPN. However the ICD10 codes listed in the policy do not accommodate diseases such as AML and glioma for which current NCCN guidelines consider testing to medically necessary. In addition the ICD10 codes for diseases such as CMML which demonstrate features of both MPN and MDS have been omitted. In addition, we request addition of ICD-10 codes associated with the appropriate clinical criteria raising the suspicion of MPN and AML or glioma that trigger the oncologist's request for this testing (e.g. D47.1 Chronic myeloproliferative disease). **We recommend inclusion of additional ICD-10 codes for MPN, AML and central nervous system glioma that would fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

Group 33 AML

C92	Myeloid leukemia
C92.0	Acute myeloblastic leukemia
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.3	Myeloid sarcoma
C92.30	Myeloid sarcoma, not having achieved remission
C92.32	Myeloid sarcoma, in relapse
C92.4	Acute promyelocytic leukemia
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.42	Acute promyelocytic leukemia, in relapse
C92.5	Acute myelomonocytic leukemia
C92.50	Acute myelomonocytic leukemia, not having achieved 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
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.9	Myeloid leukemia, unspecified
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.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved 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.Z2	Other myeloid leukemia, in relapse
C93.0	Acute monoblastic/monocytic leukemia (AMML)
C93.00	AMML not having achieved remission
C93.02	AMML in relapse
C94.0	Acute erythroid leukemia
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse
C94.8	Other specified leukemias

C94.80	Other specified leukemias not having achieved remission
C94.82	Other specified leukemias in relapse
C95	Leukemia of unspecified cell type
C95.0	Acute leukemia of unspecified cell type
C95.00	Acute leukemia of unspecified cell type not having achieved remission
C95.02	Acute leukemia of unspecified cell type in relapse
C95.9	Leukemia, unspecified
C95.90	Leukemia, unspecified not having achieved remission
C95.92	Leukemia, unspecified in relapse

Group 33 MPN

C92.2	Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
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
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D47	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D47.Z	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D72	Other disorders of white blood cells
D72.8	Other specified disorders of white blood cells
D72.82	Elevated white blood cell count
D72.821	Monocytosis (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
D75.89	Other specified diseases of blood and blood-forming organs
D75.9	Disease of blood and blood-forming organs, unspecified
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
R16	Hepatomegaly and splenomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified

Group 33 MPN/MDS (Myelodysplastic/myeloproliferative neoplasms) as defined by the WHO

C93.1	Chronic myelomonocytic leukemia (CMML)
C93.10	CMML not having achieved remission
C93.12	CMML in relapse
C93.Z	Other monocytic leukemia
C93.Z0	Other monocytic leukemia not having achieved remission

C93.Z2 Other monocytic leukemia in relapse
C93.9 Monocytic leukemia, unspecified
C93.90 Monocytic leukemia, unspecified not having achieved remission
C93.92 Monocytic leukemia, unspecified in relapse
C95.1 Chronic leukemia of unspecified cell type
C95.10 Chronic leukemia of unspecified cell type not having achieved remission
C95.12 Chronic leukemia of unspecified cell type in relapse

Group 33 Central Nervous System Gliomas

C71.0 Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1 Malignant neoplasm of frontal lobe
C71.2 Malignant neoplasm of temporal lobe
C71.3 Malignant neoplasm of perietal lobe
C71.4 Malignant neoplasm of occipital lobe
C71.5 Malignant neoplasm of cerebral ventricle
C71.6 Malignant neoplasm of cerebellum
C71.7 Malignant neoplasm of brain stem
C71.8 Malignant neoplasm of overlapping sites of brain
C71.9 Malignant neoplasm of brain, unspecified

CPT Code 81175 and 81176 (ASXL1)

ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence or targeted sequence analysis (eg, exon12) is considered medically necessary in patients with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) to guide therapeutic decision making.

Evidence: This mutation is an independent predictor of poor prognosis in MDS, MPN and in AML (except in favorable risk subtypes) acting as an essential factor in the decision whether a patient should undergo bone marrow transplant (MDS 2018 v2 NCCN guidelines, see MDS-C, MPN 2018 v2 NCCN guidelines, see MPN-D, AML 2018 v1 NCCN guidelines, see AML-A).

Group 32 ICD-10 Codes Paragraph (ASXL1)

The proposed policy lists the 17 ICD-10 codes for MDS and 3 for MPN. We agree that an exact diagnosis and ICD-10 should be known for a patient previously classified as having MDS or MPN. However the ICD10 codes listed in the policy does not accommodate AML for which current NCCN guidelines consider testing to medically necessary. In addition the ICD10 codes for diseases such as CMML which demonstrate features of both MPN and MDS have been omitted. In addition, we request addition of ICD-10 codes associated with the appropriate clinical criteria raising the suspicion of MPN, MDS or AML that trigger the oncologist's request for this testing (e.g. D70.8 other neutropenia). **We recommend inclusion of additional ICD-10 codes for MDS, MPN and AML that would fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

Group 32 AML

C92 Myeloid leukemia
C92.0 Acute myeloblastic leukemia
C92.00 Acute myeloblastic leukemia, not having achieved remission
C92.02 Acute myeloblastic leukemia, in relapse
C92.3 Myeloid sarcoma
C92.30 Myeloid sarcoma, not having achieved remission
C92.32 Myeloid sarcoma, in relapse
C92.4 Acute promyelocytic leukemia
C92.40 Acute promyelocytic leukemia, not having achieved remission
C92.42 Acute promyelocytic leukemia, in relapse
C92.5 Acute myelomonocytic leukemia

C92.50	Acute myelomonocytic leukemia, not having achieved 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
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.9	Myeloid leukemia, unspecified
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.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved 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.Z2	Other myeloid leukemia, in relapse
C93.0	Acute monoblastic/monocytic leukemia (AMML)
C93.00	AMML not having achieved remission
C93.02	AMML in relapse
C94.0	Acute erythroid leukemia
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse
C94.8	Other specified leukemias
C94.80	Other specified leukemias not having achieved remission
C94.82	Other specified leukemias in relapse
C95	Leukemia of unspecified cell type
C95.0	Acute leukemia of unspecified cell type
C95.00	Acute leukemia of unspecified cell type not having achieved remission
C95.02	Acute leukemia of unspecified cell type in relapse
C95.9	Leukemia, unspecified
C95.90	Leukemia, unspecified not having achieved remission
C95.92	Leukemia, unspecified in relapse

Group *32 MDS*

C92.2	Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
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
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D47	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D47.Z	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D72	Other disorders of white blood cells

D72.8	Other specified disorders of white blood cells
D72.82	Elevated white blood cell count
D72.821	Monocytosis (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
D75.89	Other specified diseases of blood and blood-forming organs
D75.9	Disease of blood and blood-forming organs, unspecified
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
R16	Hepatomegaly and splenomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified

Group 32 MPN

C92.2	Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
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
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D47	Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D47.Z	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D72	Other disorders of white blood cells
D72.8	Other specified disorders of white blood cells
D72.82	Elevated white blood cell count
D72.821	Monocytosis (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
D75.89	Other specified diseases of blood and blood-forming organs
D75.9	Disease of blood and blood-forming organs, unspecified
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
R16	Hepatomegaly and splenomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified

Group 32 MPN/MDS (Myelodysplastic/myeloproliferative neoplasms) as defined by the WH

C93.1	Chronic myelomonocytic leukemia (CMML)
C93.10	CMML not having achieved remission
C93.12	CMML in relapse
C93.Z	Other monocytic leukemia
C93.Z0	Other monocytic leukemia not having achieved remission
C93.Z2	Other monocytic leukemia in relapse
C93.9	Monocytic leukemia, unspecified
C93.90	Monocytic leukemia, unspecified not having achieved remission
C93.92	Monocytic leukemia, unspecified in relapse
C95.1	Chronic leukemia of unspecified cell type
C95.10	Chronic leukemia of unspecified cell type not having achieved remission
C95.12	Chronic leukemia of unspecified cell type in relapse

CPT Code 81334

RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8) is considered medically necessary in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) to guide therapeutic decision making.

Evidence: This mutation is an independent predictor of prognosis in both AML and MDS and is an essential factor in the decision whether a patient should undergo bone marrow transplant (2018 AML and MDS NCCN guidelines, Arber DA et 2016).

Group 31 ICD-10 Codes Paragraph (RUNX1)

The proposed policy lists the 17 ICD-10 codes for MDS. We agree that an exact diagnosis and ICD-10 should be known for a patient previously classified as having MDS. However the ICD10 codes listed in the policy do not accommodate AML for which current NCCN guidelines consider testing to be medically necessary. In addition the ICD10 codes for diseases such as CMML which demonstrate features of both MPN and MDS have been omitted. In addition, we request addition of ICD-10 codes associated with the appropriate clinical criteria raising the suspicion of MDS and AML that trigger the oncologist's request for this testing (e.g. D70.8 other neutropenia). **We recommend inclusion of additional ICD-10 codes for MDS and AML that would fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

Group 31 AML

C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.30	Myeloid sarcoma, not having achieved remission
C92.32	Myeloid sarcoma, in relapse
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.42	Acute promyelocytic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z2	Other myeloid leukemia, in relapse
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse
C92	Myeloid leukemia
C92.0	Acute myeloblastic leukemia
C92.3	Myeloid sarcoma

C92.4	Acute promyelocytic leukemia
C92.5	Acute myelomonocytic leukemia
C92.6	Acute myeloid leukemia with 11q23-abnormality
C92.9	Myeloid leukemia, unspecified
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.Z	Other myeloid leukemia
C94.0	Acute erythroid leukemia
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse
R16	Hepatomegaly and splenomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified
C93.0	Acute monoblastic/monocytic leukemia (AMML)
C93.00	AMML not having achieved remission
C93.02	AMML in relapse
C93.0	Acute monoblastic/monocytic leukemia (AMML)
C94.8	Other specified leukemias
C94.80	Other specified leukemias not having achieved remission
C94.82	Other specified leukemias in relapse
C95	Leukemia of unspecified cell type
C95.0	Acute leukemia of unspecified cell type
C95.00	Acute leukemia of unspecified cell type not having achieved remission
C95.02	Acute leukemia of unspecified cell type in relapse
C95.9	Leukemia, unspecified
C95.90	Leukemia, unspecified not having achieved remission
C95.92	Leukemia, unspecified in relapse

31 MDS

C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
D46	Myelodysplastic syndromes
D46.2	Refractory anemia with excess of blasts [RAEB]
D46	Myelodysplastic syndromes
D46.2	Refractory anemia with excess of blasts [RAEB]
D69	Purpura and other hemorrhagic conditions
D69.4	Other primary thrombocytopenia
D69.49	Other primary thrombocytopenia
D69.8	Other specified hemorrhagic conditions
D69.9	Hemorrhagic condition, unspecified
D72	Other disorders of white blood cells
D72.8	Other specified disorders of white blood cells
D72.81	Decreased white blood cell count
D75	Other and unspecified diseases of blood and blood-forming organs
D75.89	Other specified diseases of blood and blood-forming organs
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere
R16	Hepatomegaly and splenomegaly, not elsewhere classified
R16.1	Splenomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified

CPT Code 81479

MYD88 genetic test is considered medically necessary in patients with Waldenstrom's Macroglobulinemia (WM) and Lymphoplasmacytic lymphoma (LPL) and diffuse large B-cell cell lymphoma (DLBCL) for therapeutic decision making.

Evidence: The MYD88 L265P somatic mutation which is widely prevalent in patients with WM/LPL is useful in differentiating WM/LPL from other B-cell malignancies with overlapping clinical and pathological features. For example MYD88 mutation status is used to differentiate WM versus MZL if plasmacytic differentiation is present (2018 v2 NCCN B-cell lymphoma guidelines, see MALT1, NGMLT-1, NODE-1, SPLN-1, NHODG-A). A clinical trial of ibrutinib in previously treated patients with WM, showed fewer overall and major responses among patients with wild-type MYD88 and CXCR4 than in those with the MYD88 L265P variant and either wild-type CXCR4 or CXCR4 WHIM (Treon et al. 2015). In a phase 1 And 2 clinical trials consisting of patients with relapsed or refractory DLBCL, ibrutinib produced complete or partial responses in 37% (14/38) of patients with ABC DLBCL, but in only 5% (1/20) of subjects with GCB DLBCL. ABC DLBCL tumors with BCR mutations responded to ibrutinib frequently (5/9, 55%), especially those with concomitant myeloid differentiation primary response 88 (MYD88) mutations (4/5; 80%) (Wilson et al 2015). Additional studies indicate ibrutinib sensitivity correlates with the concomitant double mutation of CD79B and MYD8 and resistance is associated with acquisition of BTK mutation p.C481S (Wu et al 2015, Chen et al 2016).

Group 34 ICD-10 Codes Paragraph (MYD88)

The proposed policy lists the 10 ICD-10 codes for Lymphoplasmacytic lymphoma (LPL) and one code for Waldenstrom's Macroglobulinemia. We agree that an exact diagnosis and ICD-10 should be known for a patient previously classified as having WM or LPL. However the ICD10 codes listed in the policy do not accommodate the differential diagnosis of Marginal Zone Lymphoma (MZL) versus WM/LPL. NCCN guidelines dictate using MYD88 testing to categorize WM/LPL or MZL because these lymphomas have overlapping clinical and pathological features . In addition we recommend adding ICD10 codes for diffuse large B-cell cell lymphoma (DLBCL) since an MYD88 mutation may be required for ibrutinib sensitivity. **We recommend inclusion of additional ICD-10 codes for MZL and DLBCL that would fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

C85.8 **Marginal zone B-cell lymphoma** (Other specified types of non-Hodgkin lymphoma)
C85.80 …… unspecified site
C85.81 …… lymph nodes of head, face, and neck
C85.82 …… intrathoracic lymph nodes
C85.83 …… intra-abdominal lymph nodes
C85.84 …… lymph nodes of axilla and upper limb
C85.85 …… lymph nodes of inguinal region and lower limb
C85.86 …… intrapelvic lymph nodes
C85.87 …… spleen
C85.88 …… lymph nodes of multiple sites
C85.89 …… extranodal and solid organ sites
C83.3 **Diffuse large B-cell lymphoma**
C83.30 Unspecified site
C83.31 Lymph nodes of head, face, and neck
C83.32 Intrathoracic lymph nodes
C83.33 Intra-abdominal lymph nodes
C83.34 Lymph nodes of axilla and upper limb
C83.35 Lymph nodes of inguinal region and lower limb
C83.36 Intrapelvic lymph nodes
C83.37 Spleen
C83.38 Lymph nodes of multiple sites
C83.39 Extranodal and solid organ sites

CPT Code 81335 (TPMT)

TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)

Evidence:
2018 ver1 NCCN guidelines for acute lympoblastic leukemia recommend testing for TPMT gene polymorphisms particularly in patients who develop severe neutropenia after starting 6-MP chemotherapy. Factors that affect the bioavailability of 6-MP can significantly impact patient care. 6-MP can undergo thiol methylation by TPMT. Compared to the wild-type TPMT phenotype, patients who are homozygous TPMT-deficient require a 10- to 15-fold reduction in 6-MP to alleviate hematopoietic toxicity.

Group 30 ICD-10 Codes Paragraph (TPMT)
The proposed policy lists 2 ICD-10 codes for acute lymphoblastic leukemia. However these patients routinely receive a bone marrow transplant and may be treated with 6-MP therapy in relapse. Consequently we request consideration of ICD10 codes associated with bone marrow transplant. In addition 6-MP is used to control autoimmune diseases such as Crohn's disease and ulcerative colitis (REF). **We recommend inclusion of additional ICD-10 codes for these scenarios to fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

81335	**TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)**
C91.0	Chronic lymphocytic leukemia of B-cell type not achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.3	Prolymphocytic leukemia of B-cell type not achieved remission
C91.4	Hairy cell leukemia not having achieved remission
C91.5	Adult T-cell lymph/leuk (HTLV-1-assoc) not having achieved remission
C91.6	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.A	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.Z	Other lymphoid leukemia not having achieved remission
K50.00	Crohn's disease of small intestine
Z94	Transplanted organ and tissue status

Human Platelet Antigen Genotyping (CPT codes 81105 – 81112)

We recommend the addition of CPT codes 81105-81112 as genotyping for human platelet antigens is important for identifying woman at risk for neonatal alloimmune thrombocytopenia (NAIT). Post-transfusion purpura is an immune reaction against human platelet antigens, often occurring when a woman is sensitized during pregnancy, then subsequently receives a transfusion. Performing HPA genotyping can confirm the cause of severe thrombocytopenia presentation in women, and once identified, she is transfused with only compatible platelets. Medicare beneficiaries of child-bearing age should be tested (or their fetus should be tested) if there has been a previous affected pregnancy or the fetus/neonate is suspected to have neonatal alloimmune thrombocytopenia (NAIT). NAIT may be more severe in subsequent pregnancies, and identifying platelet incompatibility by genotyping a fetus determines the risk to the pregnancy, the need to monitor or offer antenatal therapy (IVIG and prednisone) and whether Caesarean delivery is recommended. We recognize that there will be very few Medicare beneficiaries for whom this testing will be clinically actionable, but still urge you to ensure these beneficiaries have access to this critical testing. Reference: Br J Haematol. 2013 Apr; 161(1): 3–14.

With regard to these new CPT category one codes, we request that NGS consider adding the following additional ICD-10 diagnosis codes to the final policy.

D69	Purpura and other hemorrhagic conditions
D69.51	Postransfusion purpura
D69.1	Qualitative platelet defects
D69.3	Immune thrombocytopenic purpura
D69.4	Other primary thrombocytopenia
D69.42	Congenital and hereditary thrombocytopenia purpura
D69.49	Other primary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D69.8	Other specified hemorrhagic conditions
D69.9	Hemorrhagic condition, unspecified

Pharmacogenetics Codes (CPT codes 81283 (IFNL3), 81247-81249 (G6PD), 81335 (TPMT), 81328 (SLC01B1))

With regards to codes 81283 (IFNL3), 81247-81249 (G6PD), 81335 (TPMT), and 81328 (SLC01B1), which are related to pharmacogenetics testing, AMP and CAP urge you to accept the recommendations provided by the Implementing Genomics in Practice (IGNITE) Consortium which were formulated by members of our organizations and reflect their concerns. (Appendix A)

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.

Association for Molecular Pathology
College of American Pathologists

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April 9, 2018

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IGNITE Response to Proposed LCD

The Implementing Genomics in Practice (IGNITE) Consortium is a National Human Genomics Research Institute (NHGRI)-funded research group that is implementing genome-informed personalized healthcare in clinical settings to advance the practice, delivery and economics of health care. While personalized medicine is transforming the health system as we know it, we are bridging the gap between genomics research and patient care.

Knowledge related to pharmacogenetic testing is ripe for translation into practice. Drug therapy for many conditions is currently plagued by an unacceptable level of adverse drug reactions, inefficacy, and poor compliance. Adverse drug reactions are responsible for the death of approximately 100,000 patients per year, and are also the cause of over 2,216,000 hospitalizations per year. This is one of several reasons for poor compliance and adherence to many therapeutic drugs, which ultimately reduces drug efficacy and worsens the societal disease burden. Genomic science has the potential to change this. For many of the most commonly used drugs, the specific genetic variants that result in either toxic adverse reactions or sustained efficacy are now known. The use of genetic testing for improving drug efficacy and reducing adverse drug reactions is now endorsed by many expert organizations. The FDA has placed genetic testing recommendations and black box warnings in 121 labels. Guidelines are being written for gene-drug pairs for which there is overwhelming evidence for the benefit of using genetic testing during drug therapy. For example, the Clinical Pharmacogenetics Implementation Consortium (CPIC), a working group of investigators from the NIH Pharmacogenomics Research Network, has published guidelines for using pharmacogenetic data in the prescribing of commonly used drugs, and more are in development. These guidelines are being endorsed by the American Society of Health-System Pharmacists, Association for Molecular Pathology and are accepted into the guidelines.gov website. In addition, the Dutch Pharmacogenomics Working Group has also written guidelines for drugs.

Preemptive pharmacogenetic testing may reduce health care system. Thus we support guideline-based Pharmacogenomic testing.

CPIC: Guidelines (https://cpicpgx.org/guidelines/), see website for most current information

DRUGS	GENES	GUIDELINES
abacavir	HLA-B	*guideline*
allopurinol	HLA-B	*guideline*
amitriptyline	CYP2C19 CYP2D6	*guideline*
atazanavir	UGT1A1	*guideline*
azathioprine	TPMT	*guideline*
capecitabine	DPYD	*guideline*
carbamazepine	HLA-A HLA-B	*guideline*
citalopram escitalopram	CYP2C19	*guideline*
clomipramine	CYP2C19 CYP2D6	*guideline*
clopidogrel	CYP2C19	*guideline*
codeine	CYP2D6	*guideline*
desipramine	CYP2D6	*guideline*
doxepin	CYP2C19 CYP2D6	*guideline*
fluorouracil	DPYD	*guideline*
fluvoxamine	CYP2D6	*guideline*
imipramine	CYP2C19 CYP2D6	*guideline*
ivacaftor	CFTR	*guideline*
mercaptopurine	TPMT	*guideline*
nortriptyline	CYP2D6	*guideline*
ondansetron	CYP2D6	*guideline*
oxcarbazepine	HLA-B	*guideline*
paroxetine	CYP2D6	*guideline*
peginterferon alfa-2a peginterferon alfa-2b ribavirin	IFNL3	*guideline*
phenytoin	CYP2C9 HLA-B	*guideline*
rasburicase	G6PD	*guideline*

sertraline	CYP2C19	*guideline*
simvastatin	SLCO1B1	*guideline*
tacrolimus	CYP3A5	*guideline*
tamoxifen	CYP2D6	*guideline*
tegafur	DPYD	*guideline*
thioguanine	TPMT	*guideline*
trimipramine	CYP2C19 CYP2D6	*guideline*
tropisetron	CYP2D6	*guideline*
voriconazole	CYP2C19	*guideline*
warfarin	CYP2C9 CYP4F2 VKORC1	*guideline*

81283 (IFNL3)

We disagree with the conclusions in the LCD as the evidence supports that genotyping for *IFNL3* (IL28B) variation (rs12979860) is the strongest baseline predictor of response to PEG-interferon-alpha-containing regimens in HCV genotype 1 patients. Patients with the favorable response genotype (rs12979860 CC) have increased likelihood of response (higher sustained viral response rate) to PEG-interferon-alpha-containing regimens as compared to patients with unfavorable response genotype (rs12979860 CT or TT). We do acknowledge that newer treatment regimens are replacing PEG-interferon therapies. Given the level of evidence identified in the CPIC evaluation and the guideline recommendations for modification of treatment based on the *IFNL3* (IL28B) status, we believe the criterion that a test result have an impact on the patient's management (i.e., clinical utility) has been met.

81247-81249 (G6PD) (adapted from https://www.pharmgkb.org/vip/769255834)

We disagree with the conclusions in the LCD as the evidence supports that genotyping and phenotyping are important for heterozygous females for G6PD deficiency. The medical profession has known for more than 2000 years that the ingestion of fava beans can have dire consequences in some individuals, however, it wasn't until the 20th century that a deficiency in the G6PD enzyme was discovered to be the underlying cause of 'Favism', and the connection that agents other than fava beans can cause similar adverse events in G6PD deficient individuals.

Exogenous agents can trigger hemolytic anemia in G6PD deficient individuals by inducing oxidative stress in RBCs. These include certain food items, therapeutic drugs, infections, and exposure to chemicals. G6PD variants have been classified into 5 WHO categories according to the severity of clinical manifestation resulting from the genotype (see Table 1), with class II and III the most common type of polymorphic G6PD deficient variant. Due to lower RBC G6PD activity, patients carrying class I sporadic variants (associated with CNSHA) are highly susceptible to hemolytic anemia caused by the same drugs that can induce adverse reactions in carriers of polymorphic G6PD variants (reviewed in PMID: 17611006).

Table 1: WHO Classification of *G6PD* variants

WHO Class	Enzyme Activity	Associated Phenotype	Variant Example
I	severe deficiency	Congenital Non-Spherocytic Hemolytic Anemia (CNSHA)	Tondela, Palermo
II	<10% severely deficient	Risk of acute hemolytic anemia	Mediterranean, Canton
III	10-60% moderate deficiency	Risk of acute hemolytic anemia	A- Haplotype, Asahi
IV	60-150% normal activity	No clinical manifestations	B (wildtype), A
V	150% enhanced activity		Hektoen

Testing for G6PD deficiency

G6PD variants that result in enzyme deficiency confer a G6PD deficient phenotype in hemizygous males (with one copy of the G6PD gene) and homozygous (or compound heterozygous) females. To diagnose a phenotype of G6PD deficiency in heterozygous females is more difficult, as the extent of enzyme deficiency activity can vary greatly within heterozygous individuals, due to X-linked mosaicism. This pattern of gene inactivation is random therefore female heterozygotes will have G6PD deficient RBCs combined with those expressing normal G6PD activity, and the population sizes of these cells can vary from 50:50, to minimal levels or a majority of G6PD deficient cells. Genotyping is therefore essential to establish heterozygosity in females; however this can make prediction of drug response difficult without phenotypic information of G6PD enzyme activity levels. For example, 75% of females genetically heterozygous for the Mediterranean variant had normal G6PD activity, whereas 25% were enzyme deficient, as assessed by a colorimetric test. Testing for both genotype and enzyme function is the ideal method.

G6PD and therapeutic drug response

The WHO recommends testing of drugs to predict for risk of hemolysis in G6PD deficient individuals if the drugs are to be prescribed in areas of high prevalence of G6PD deficiency. As a consequence of adverse reactions in individuals with G6PD deficiency, the FDA has introduced warnings or precautions on the drug labeling of primaquine, chloroquine, dapsone, rasburicase, avandaryl tablets (glimepiride + rosiglitazone maleate) and glucovance tablets (metformin + glibenclamide) (FDA website). These highlight the possible risk of hemolytic anemia in G6PD deficient individuals upon drug intake. It should be noted that numerous factors can contribute to drug-induced hemolytic anemia in G6PD deficient individuals, including high dosage, other drugs taken in combination, concurrent infections and other genetic variants. Therefore it may be that many drugs which have been reported to cause hemolysis in individual case studies can be taken safely by G6PD deficient individuals, for example aspirin, vitamin C and chloroquine. These drugs however should be administered with caution especially in combination with other drugs or at high doses, with possible monitoring of RBC or hemoglobin levels. Readdressing the safety of drugs in these individuals could make effective therapeutics available. More information and comprehensive advice on unsafe drugs in G6PD deficient individuals can be found at http://www.favism.org.

Given the level of evidence identified in the CPIC evaluation and the WHO and FDA recommendations for modification of treatment based on the G6PD status, we believe the criterion that a test result have an impact on the patient's management (i.e., clinical utility) has been met.

81335 TPMT (adapted from https://www.pharmgkb.org/vip/769173911)

We disagree with the conclusions in the LCD as the evidence supports that genotyping for TPMT.

Genetic variants in *TPMT* have been shown to be an important factor in individual variations in response to thiopurine drug therapy. 6-MP is inactivated, in part, by S-methylation, catalyzed by TPMT. An alternative "metabolic activation" process leads to the formation of cytotoxic 6-thioguanine nucleotides (6-TGN). In addition, 6-MP is metabolized to methyl-thioinosine monophosphate, which inhibits *de novo* purine synthesis, adding another mechanism of cytotoxicity.

Lennard *et al.* (1987, 1990) showed that, in the children with acute lymphoblastic leukemia (ALL) who were treated with 6-MP, red cell 6-TGN correlated inversely with RBC *TPMT* activity (*i.e*., the lower the level of S-methylation, the more drug would be available for metabolism to form the cytotoxic 6-TGNs). It was also demonstrated that subjects with very low RBC (red blood cell) *TPMT* (*i.e*., those homozygous for that trait) were at greatly increased risk for life-threatening myelosuppression when they were treated with "standard" doses of thiopurine drugs. Conversely, patients with ALL who had 6-TGN concentrations below the group mean had higher *TPMT* activities and a higher subsequent relapse rate. Individuals heterozygous for functional variants exhibited intermediate tolerance of 6-MP (*i.e.* intermediate between that observed for homozygous deficient and homozygous wildtype patients). RBC *TPMT* levels have been found to correlate with levels in other tissues such as liver, kidney, and lymphocytes. Therefore, the *TPMT* genetic polymorphism is a significant factor responsible for serious adverse drug reactions (myelosuppression) in patients treated with thiopurines and may also contribute to individual variation in therapeutic efficacy. *TPMT* genotyping is standard of care in children with acute lymphoblastic leukemia.

Thiopurine therapy plays a role in the treatment of autoimmune diseases, inflammatory bowel diseases, lupus, transplantation, and acute lymphoblastic leukemia. Given the level of evidence identified in the CPIC evaluation and the guideline recommendations for modification of treatment based on the *TPMT* status, we believe the criterion that a test result have an impact on the patient's management (i.e., clinical utility) has been met.

81346 (TYMS) (adapted from https://www.pharmgkb.org/vip/769172754)

Thymidylate synthase (TYMS) catalyses the methylation of dUMP to dTMP. As the sole de novo source of thymidylate in the cell, it is an important target for drugs such as 5-fluorouracil and methotrexate. Since there is not strong evidence to support clinical utility, we agree that *TYMS* testing should not be covered at this time.

Reconsideration for 81328 *SLCO1B1* (adapted from https://www.pharmgkb.org/vip/769173594)

We request reconsideration for 81328 given the level of evidence identified in the CPIC evaluation and the guideline recommendations for modification of treatment based on the

SLCO1B1 status, we believe the criterion that a test result have an impact on the patient's management (i.e., clinical utility) has been met.

The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene encodes for a membrane-bound sodium-independent organic anion transporter protein (OATP1B1) that is involved in active cellular influx of many endogenous and xenobiotic compounds, especially the HMG-CoA reductase inhibitors (statins) because statins are widely prescribed for cardiovascular disease (CVD) risk reduction. OATP1B1 transport is particularly important for hepatic accessibility of pravastatin, as this compound is too hydrophilic to gain significant heptocellular entry through passive transport. *SLCO1B1* variants are associated with simvastatin-induced myopathies.

REQUEST:

- **For the indications that we have above, we request that the ICD10 codes be expanded**
- **Include ICD10, T78.40, T80-T88, T88.7 for drug allergy not-otherwise specified**
- T36 Poisoning by, adverse effect of and underdosing of systemic antibiotics
- T37 Poisoning by, adverse effect of and underdosing of other systemic anti- infectives and antiparasitics
- T38 Poisoning by, adverse effect of and underdosing of hormones and their synthetic substitutes and antagonists, not elsewhere classified
- T39 Poisoning by, adverse effect of and underdosing of nonopioid analgesics, antipyretics and antirheumatics
- T40 Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics [hallucinogens]
- T41 Poisoning by, adverse effect of and underdosing of anesthetics and therapeutic gases
- T42 Poisoning by, adverse effect of and underdosing of antiepileptic, sedative- hypnotic and antiparkinsonism drugs
- T43 Poisoning by, adverse effect of and underdosing of psychotropic drugs, not elsewhere classified
- T44 Poisoning by, adverse effect of and underdosing of drugs primarily affecting the autonomic nervous system
- T45 Poisoning by, adverse effect of and underdosing of primarily systemic and hematological agents, not elsewhere classified
- T46 Poisoning by, adverse effect of and underdosing of agents primarily affecting the cardiovascular system

- T47 Poisoning by, adverse effect of and underdosing of agents primarily affecting the gastrointestinal system
- T48 Poisoning by, adverse effect of and underdosing of agents primarily acting on smooth and skeletal muscles and the respiratory system
- T49 Poisoning by, adverse effect of and underdosing of topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinorlaryngological and dental drugs
- T50 Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances

We respectfully ask that you consider our comments which were prepared by providers in the IGNITE consortium, laboratory directors, and staff who provide service to Medicare beneficiaries covered by NGS. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this DLCD. Please direct your correspondence to Dr. V.M. Pratt. Ph.D, FACMG.

Sincerely,

V.M. Pratt, Ph.D, FACMG

On behalf of the IGNITE Consortium

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