December 15, 2019

Debra Patterson, MD
Medical Director
Novitas Solutions Medical Policy Department
Suite 400
707 Grant Street
Pittsburg, PA 15219

Submitted electronically at: ProposedLCDComments@novitas-solutions.com

RE: Biomarkers for Oncology (DL35396)

Dear Dr. Patterson,

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 Novitas' proposed coverage policy regarding Biomarkers for Oncology (DL35396).

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 both of our organizations share the same perspective regarding this draft local coverage determination (LCD). We appreciate the effort that has gone into the development of this proposed LCD, and we offer the following recommendations for Novitas' consideration. This comment letter will focus primarily on the leukemia disease classes and biomarkers addressed in this draft policy.

Coverage Indications

Molecular Tests

Leukemias and Lymphomas

AMP and CAP appreciate that Novitas addressed issues related to coverage of specific leukemia and lymphoma biomarkers and proposed coverage for the following conditions:

- Acute lymphoid leukemia (ALL)
- Hairy cell leukemia

- Aplastic anemia
- Follicular Lymphoma
- Hypereosinophilia Syndrome
- Mantle cell lymphoma
- Mastocytosis
- T-cell prolymphocytic leukemia (TLGLL)
- T-cell large granular lymphocytic leukemia (TLGLL)
- Cytogenomic microarray analysis
- Waldenstrom's Lymphoplasmacytic Lymphoma

Our additional recommendations regarding coverage are described below:

- Acute myeloid leukemia (AML, and including acute promyelocytic leukemia)

  AMP and CAP support Novitas' decision to cover ASXL1, KIT, TP53, RUNX1, and TET2. We also recommend covering GATA2 and WT1 to comply with the 2016 WHO guidelines for diagnosis and prognosis of certain acute myeloid leukemias (Swerdlow, SH et al, 2016).

- Burkitt's Lymphoma

  AMP and CAP support Novitas' decision to cover IGH and TP53. Please also consider covering testing for Epstein-Barr virus (EBV) as clinical utility has been proven in this population (Gulley and Tang, 2008).

- Myeloproliferative diseases (MPD – essential thrombocytosis [ET], myelobifrosis and polycythemia vera [PV])

  Novitas lists TP53 indicated in AML and MPD only. AMP and CAP are concerned that this is restricting coverage for other myeloid disorders. **Therefore, we request that Novitas provide coverage of TP53 for all myeloid disorders including myelodysplastic syndrome (MDS) and MDS/MPN.** Supporting evidence for TP53 in MDS and MDS/MPN are provided in the myelodysplastic syndrome section below.

- Chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML)

  AMP and CAP support Novitas' decision to cover the following biomarkers: ABL1, KRAS, NRAS, BCR/ABL1, ABL1, FLT3 ITD, FLT3 D835, KIT, JAK2. We request that Novitas also consider coverage for ASXL1 testing, as these mutations are an independent adverse prognostic indicator.

- Chronic lymphoid leukemia (CLL)

  We appreciate Novitas' proposed coverage for CLL, however we request that you consider adding coverage for the following prognostic biomarkers: SF3B1 and NOTCH1 (NCCN Oncology Guidelines: Non-Hodgkin's Lymphoma; Baliakas and Hadzidimitriou, 2014; Nadeu and Delgado, 2016; Rossi and Rasi, 2012; Villamore and Conde, 2012).

- Myelodysplastic syndrome (MDS)

  We agree with Novitas' proposed coverage for prognostic biomarkers, however we request that you consider coverage for the following analytes: RUNX1, GATA2, TP53, ETV6, SF3B1, SRSF2, U2AF1, ZRSR2, CBL, SETBP1 (Haase et al, 2019; Kim et al., 2018; Steesma, D 2018; Hou et al., 2018; Gangat et al. 2018; Tefferi et al., 2017; Nazha et al., 2017; Chang et al, 2017; and Welsh et al., 2016). These have all been recommended for use by the NCCN (NCCN Clinical Guidelines: Myelodysplastic syndrome and/or WHO classification).

Coverage Limitations

AMP and CAP have concerns with several of the coverage limitations included in the draft LCD, as described below. There is a growing body of evidence demonstrating the value of multiplex NGS tests throughout the duration of a patient's treatment, as a multigene panel using NGS checks for a variety of clinically important mutations that lead to improved decision making on the appropriate targeted therapies for a patient.[1] If testing is limited to one NGS-based test per patient, providers may be prevented from identifying the appropriate therapy over the course of the patient's treatment.

Novitas only provides coverage for certain tests once per lifetime per beneficiary. The following tests are proposed to be covered once per lifetime per beneficiary:

- Brain Molecular Biomarkers
- Hereditary neuroendocrine tumor disorders
- Hereditary neuroendocrine tumor disorders; duplication/deletion analysis
- ThyraMIR, Afirma, ThyGeNEXT, RosettaGX Reveal and ThyroSeq tests
  - Should the unlikely situation of a second, unrelated thyroid nodule with indeterminate pathology occur, coverage may be considered upon appeal with supporting documentation
  - TUO CTID (Cancer TYPE ID)

AMP and CAP disagree with the strict limitation of repeat testing for these tests and we ask that Novitas also allow repeat testing for these cancers, when medically reasonable and necessary. Novitas acknowledges that there are some tumor specific scenarios where repeat testing would be necessary:

> "While some biomarkers have utility for testing once per lifetime, there are some tumor specific scenarios where repeat testing would be needed for assessment of response to therapy or to identify basis of disease progression. In cases with metastatic or recurrent tumors, repeat testing may be useful in determining further clinical management. Also, biomarkers such as BCR-ABL1 fusion, PML-RARA fusion are useful in monitoring response to therapy and predict a response up to four times per annum."

While Novitas recognizes that there are circumstances that warrant repeat testing, such as recurrence of disease and changes in behavior of disease, there are additional circumstances that may warrant more than one NGS test, such as assessment of both germline and somatic mutations as well as minimal residual disease assessment. Hematologic cancer guidelines support MRD assessment at relevant points in a patient's cancer care (See and Press et al, 2019). The most recent NCCN guidelines for multiple myeloma include response

[1] NCCN Guidelines version 3.2019, Genetic/Familial High-Risk Assessment. Multi-Gene Testing.

criteria that support the use of tests using NGS technology to identify MRD, and they recommend testing for MRD after each treatment stage (NCCN Guidelines, Multiple Myeloma 2019). Recent NCCN guidelines for acute lymphoblastic leukemia (ALL) also reference NGS methods for disease assessment in adults at baseline and following different treatment phases (NCCN Guidelines, Acute Lymphoblastic Leukemia, 2019).

Furthermore, this strict limitation would apply to tests for both germline and somatic mutations, even when the patient may require more than one NGS-based test for the provider to properly diagnose and manage their treatment. There are many situations in which a person is diagnosed with cancer and the oncologist orders somatic NGS-based testing. If a mutation is found that is also implicated in inherited cancers, such as a mutation in a *BRCA* gene, the standard practice is to refer the patient for germline testing to determine if the mutation is inherited in order to properly treat and manage the patient's cancer.

Documentation Requirements

Among several others, Novitas proposes the following documentation requirement:

> "The Medical record documentation must support the medical necessity of the services as stated in this policy. Specifically, the medical record should reflect whether any biomarker ordered is diagnostic, prognostic or predictive, as well as be able to clearly correlate any test results with given interventions (e.g., particular selection of chemotherapy)."

AMP and CAP are concerned that it would be difficult for many laboratories, including commercial reference laboratories, to complete the proposed documentation requirements. In most instances, commercial reference laboratories do not have access to the patient's medical record, which would make obtaining the proper documentation for coverage exceedingly difficult, if not impossible.

We agree that physicians should document medical necessity for any testing in the patient's medical record, as part of good medical care, however, tying the documentation to coverage is difficult for laboratories, particularly commercial reference laboratories. We recommend that Novitas remove this requirement as it is unworkable with how testing is ordered. Additionally, we fear that such requirements may prevent physicians to order biomarkers based on this level of justification required, thereby potentially restricting patients' access to appropriate testing.

CPT Coding

Most myeloid panels include anywhere from 50-95 genes. For example, a large number of genes are required to properly diagnose complex cases, such as myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), overlap myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukemia (AML). **Therefore, we recommend that Novitas expand coverage to include panels with 51 or more genes, as represented by CPT code 81455.**

Upon request, we would be happy to furnish several examples of commercially available test examples which are supplied by CLIA labs in Novitas jurisdictions H and L. For these reasons, AMP and CAP believe that a panel with 51 or more genes is necessary to properly advise patient treatment options, patients and coverage should be expanded accordingly.

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 DA52986 including, but not be limited to the following list:

C88.8 Other malignant immunoproliferative diseases
C92.2 Atypical chronic myeloid leukemia, BCR/ABL-negative
C92.20 Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.21 Atypical chronic myeloid leukemia, BCR/ABL-negative, in remission
C92.22 Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
C93 Monocytic leukemia
C93.1 Chronic myelomonocytic leukemia
C93.10 Chronic myelomonocytic leukemia not having achieved remission
C93.11 Chronic myelomonocytic leukemia, in remission
C93.12 Chronic myelomonocytic leukemia, in relapse
C93.3 Juvenile myelomonocytic leukemia
C93.30 Juvenile myelomonocytic leukemia, not having achieved remission
C93.31 Juvenile myelomonocytic leukemia, in remission
C93.32 Juvenile myelomonocytic leukemia, in relapse
C93.Z Other monocytic leukemia
C93.Z0 Other monocytic leukemia, not having achieved remission
C93.Z1 Other monocytic leukemia, in remission
C93.Z2 Other monocytic leukemia, 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
C94.6 Myelodysplastic disease, not classified
D47 Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.0 Mast cell neoplasms of uncertain behavior
D47.02 Systemic mastocytosis
D47.09 Other mast cell neoplasms of uncertain behavior
D47.1 Chronic myeloproliferative disease
D47.3 Essential (hemorrhagic) thrombocythemia
D47.Z Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.9 Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D61.81 Pancytopenia
D61.810 Antineoplastic chemotherapy induced pancytopenia
D61.811 Other drug-induced pancytopenia
D61.818 Other pancytopenia
D69.4 Other primary thrombocytopenia
D69.42 Congenital and hereditary thrombocytopenia purpura

D69.49 Other primary thrombocytopenia
D69.5 Secondary thrombocytopenia
D69.59 Other secondary thrombocytopenia
D69.6 Thrombocytopenia, unspecified
D72 Other disorders of white blood cells
D72.8 Other specified disorders of white blood cells
D72.81 Decreased white blood cell count
D72.810 Lymphocytopenia
D72.82 Elevated white blood cell count
D72.821 Monocytosis (symptomatic)
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
D75.1 Secondary polycythemia
D75.81 Myelofibrosis
D75.82 Heparin induced thrombocytopenia (HIT)
D75.89 Other specified diseases of blood and blood-forming organs
D75.9 Disease of blood and blood-forming organs, unspecified

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

References

Baliakas, P., & Hidzidimitriou, A. (2014). Recurrent mutations refine prognosis in chronic lymphocytic leukemia. Leukemia, 29(2), 329-336. doi:10.1038/leu.2014.196.

Chang CK, Zhao YS, Xu F, Guo J, Zhang Z, He Q, Wu D, Wu LY, Su JY, Song LX, Xiao C, Li X. TP53 mutations predict decitabine-induced complete responses in patients with myelodysplastic syndromes. Br J Haematol. 2017 Feb;176(4):600-608. doi: 10.1111/bjh.14455. Epub 2016 Dec 16. PubMed PMID: 27984642.

Gangat N, Mudireddy M, Lasho TL, Finke CM, Nicolosi M, Szuber N, Patnaik MM, Pardanani A, Hanson CA, Ketterling RP, Tefferi A. Mutations and prognosis in myelodysplastic syndromes: karyotype-adjusted analysis of targeted sequencing in 300 consecutive cases and development of a genetic risk model. Am J Hematol. 2018 May;93(5):691-697. doi: 10.1002/ajh.25064. Epub 2018 Feb 24. PubMed PMID: 29417633.

Gulley, M.L., Tang, W., et al (2008) Laboratory Assays for Epstein-Barr Virus-Related Disease. The Journal of Molecular Diagnostics, 10(4), 279-292. doi:10.2353/jmoldx.2008.080023.

Haase D, Stevenson KE, Neuberg D, Maciejewski JP, Nazha A, Sekeres MA, Ebert BL, Garcia-Manero G, Haferlach C, Haferlach T, Kern W, Ogawa S, Nagata Y, Yoshida K, Graubert TA, Walter MJ, List AF, Komrokji RS, Padron E, Sallman D, Papaemmanuil E, Campbell PJ, Savona MR, Seegmiller A, Adès L, Fenaux P, Shih LY, Bowen D, Groves MJ, Tauro S, Fontenay M, Kosmider O, Bar-Natan M, Steensma D, Stone R, Heuser M, Thol F, Cazzola M, Malcovati L, Karsan A, Ganster C, Hellström-Lindberg E, Boultwood J, Pellagatti A, Santini V, Quek L, Vyas P, Tüchler H, Greenberg PL, Bejar R; International Working Group for MDS Molecular Prognostic Committee. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. Leukemia. 2019 Jul;33(7):1747-1758. doi: 10.1038/s41375-018-0351 2. Epub 2019 Jan 11. PubMed PMID: 30635634; PubMed Central PMCID: PMC6609480.

Hou HA, Tsai CH, Lin CC, Chou WC, Kuo YY, Liu CY, Tseng MH, Peng YL, Liu MC, Liu CW, Liao XW, Lin LI, Yao M, Tang JL, Tien HF. Incorporation of mutations in five genes in the revised International Prognostic Scoring System can improve risk stratification in the patients with myelodysplastic syndrome. Blood Cancer J. 2018 Apr 4;8(4):39. doi: 10.1038/s41408-018-0074-7. PubMed PMID: 29618722; PubMed Central PMCID: PMC5884776.

Kim YJ, Jung SH, Hur EH, Choi EJ, Lee KH, Yim SH, Kim HJ, Kwon YR, Jeon YW, Lee SH, Chung YJ, Lee JH. TP53 mutation in allogeneic hematopoietic cell transplantation for de novo myelodysplastic syndrome. Leuk Res. 2018 Nov;74:97-104. doi: 10.1016/j.leukres.2018.10.004. Epub 2018 Oct 11. PubMed PMID: 30343213.

Nadeu, F., & Delgado, J. (2016). Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. Blood, 127(17), 2122-2130. doi:10.1182/blood-2015-07- 659144.

Nazha A, Bejar R. Molecular Data and the IPSS-R: How Mutational Burden Can Affect Prognostication in MDS. Curr Hematol Malig Rep. 2017 Oct;12(5): 461-467.doi: 10.1007/s11899-017-0407-9. Review. PubMed PMID: 28844082.

NCCN Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version 2.2019 (May 15, 2019) at ALL-F.

NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma, Version 2.2019 (Nov. 16, 2019) at MYEL-D 1, 3.

Rossi, D., & Rasi, S. (2012). Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood, 121(8), 1403-1412. doi:10.1182/blood-2012-09-458265.

See, E.G., Press, RD et al. NGS-defined minimal residual disease before stem cell transplantation predicts acute myeloid leukemia response. Am J Hematol. 2019 May 23. doi:10.1002/ajh.25514.

Steensma DP. Myelodysplastic syndromes current treatment algorithm 2018. Blood Cancer J. 2018 May 24;8(5):47. doi: 10.1038/s41408-018-0085-4. Review. PubMed PMID: 29795386; PubMed Central PMCID: PMC5967332.

Swerdlow, S et al., (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016 May 19; 127(20): 2375–2390. doi: 10.1182/blood-2016-01-643569.

Tefferi A, Lasho TL, Patnaik MM, Saeed L, Mudireddy M, Idossa D, Finke C, Ketterling RP, Pardanani A, Gangat N. Targeted next-generation sequencing in myelodysplastic syndromes and prognostic interaction between mutations and IPSS-R. Am J Hematol. 2017 Dec;92(12):1311-1317. doi: 10.1002/ajh.24901. Epub 2017 Oct 20. PubMed PMID: 28875545.

Villamor, N., & Conde, L. (2012). NOTCH1 mutations identify a genetic subgroup of chronic lymphocytic leukemia patients with high risk of transformation and poor outcome. Leukemia, 27(5), 1100-1106. doi:10.1038/leu.2012.357.

Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, Wilson RK, Baty JD, Duncavage EJ, Tandon B, Lee YS, Wartman LD, Uy GL, Ghobadi A, Tomasson MH, Pusic I, Romee R, Fehniger TA, Stockerl-Goldstein KE, Vij R, Oh ST, Abboud CN, Cashen AF, Schroeder MA, Jacoby MA, Heath SE, Luber K, Janke MR, Hantel A, Khan N, Sukhanova MJ, Knoebel RW, Stock W, Graubert TA, Walter MJ, Westervelt P, Link DC, DiPersio JF, Ley TJ. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. N Engl J Med. 2016 Nov 24;375(21):2023-2036. doi:10.1056/NEJMoa1605949. PubMed PMID: 27959731; PubMed Central PMCID: PMC5217532.