June 11, 2018

Olatokunbo Awodele, M.D,
MPH 2525 No. 117th Avenue,
Suite 200
Omaha, NE 68164

Re: Draft Local Coverage Determination: MolDX: Comprehensive Genomic Profiling to Guide Treatment in Patients with Metastatic Colorectal Cancer (DL37222)

Dear Dr. Awodele,

Thank you for this opportunity to respond to your draft local coverage determination regarding MolDX: Comprehensive Genomic Profiling (CGP) to Guide Treatment in Patients with Metastatic Colorectal Cancer (DL37222). The Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 2,300 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 and commercial clinical laboratories, community hospitals, 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.

Proposed Coverage for Comprehensive Genomic Profiling

AMP and CAP applaud WPS for proposing coverage for comprehensive genomic profiling (CGP), which typically uses next generation sequencing (NGS)-based strategies. The National Comprehensive Cancer Network (NCCN) guidelines are updated on an annual basis and are based on the most current medical evidence. The NCCN 2018 guidelines for colorectal cancer agree that multi-gene testing, typically performed with next generation sequencing (NGS), is indicated in many patients with colorectal cancer (NCCN 2018). However, despite the consensus clinical benefits of NGS-based CGP, we believe that this draft LCD proposal is unreasonably restrictive, and we would like to work with you to improve coverage policy for patients with metastatic colorectal carcinoma
– most of whom would be inappropriately denied CGP coverage under this overly stringent draft policy.

As drafted, AMP and CAP experts believe this policy will severely restrict patient access to testing, given the extremely specific and unjustified testing requirements. If the draft LCD remains unchanged, for all practical purposes it is applicable to only a very limited number of laboratories in the entire country. Our comments outline changes supported by the medical literature that would broaden this restrictive testing criteria so that more high-quality, stringently compliant laboratories would also be able offer this clinically-proven testing to their patients.

We have found no evidence in the scientific literature that many of the requirements outlined in this policy will improve clinical decisions. Limiting coverage to the very small number of labs currently meeting these criteria will significantly restrict access to testing without a justifiable improvement in clinical decision making – and could, unintentionally, even worsen outcomes by delaying or preventing the genomic tests that often inform optimal therapies. In addition to the limitations in patient access to testing that will be caused by this overly stringent policy, the concomitant lack of competition in the testing space could also lead to a downturn in quality and an increase in testing costs. Furthermore, clinical research trials into new targeted cancer therapies will become more expensive and available in fewer locations due to the restricted access to testing and lack of competition.

We also remain very concerned, as detailed in previous LCD responses, about whether WPS has the statutory authority to regulate LDTs (and their analytical and clinical validity), which typically falls under the purview of CLIA.

CGP Test Description

In the policy, CGP analysis is defined as a single test using tumor tissue only (i.e., not matched tumor and normal) that can detect all six classes of genomic alterations in a single test. WPS states that other non-NGS testing platforms may be considered if they can similarly detect all classes of alterations and genomic information with comparable test performance as CGP.

We believe that requiring the detection of all six classes of genomic alterations (base pair substitutions, small indels, copy number alterations, rearrangements, tumor mutational burden [TMB], and microsatellite instability [MSI]) is not necessary, is overly burdensome to laboratories that use alternative technical approaches to provide the comparable findings, and does little to guide treatment and increase benefit to the patient. Medical necessity must be paramount in any coverage determination and the medical necessity for detecting all 6 classes of genomic alterations has not been rigorously established. Moreover, there is no medical literature that suggests multiple genomic aberrations need to be detected by a "single test", as mandated on page 4 of the draft LCD. For example, there are technologies such as SNP-based microarray that can detect genome wide copy number alterations in a sensitive and cost-efficient fashion. Targeted translocations and copy number alterations can also be detected by FISH and PCR-based methods. **We, therefore, recommend altering this policy to:**

1. **NOT require the detection of all 6 classes of genomic alterations;**
2. **NOT require the detection of all of these alterations in a single assay, and**
3. **Allow coverage consideration for laboratories that incorporate diverse and complimentary multi-test (not "single test") technologies to analogously assess for clinically relevant genomic aberrations.**

Recommendations Regarding the Proposed Coverage Requirements

AMP and CAP are supportive of Palmetto's proposal to cover CGP analysis using multiplex or NGS technology, recognizing that this testing is reasonable and necessary to guide targeted and/or immuno-oncology therapy in patients with metastatic colorectal cancer. However we disagree that all ten of the criteria listed in the draft LCD must be met and combined into a "single test" to qualify as medically necessary. As detailed above, these overly stringent criteria will limit CGP testing for CRC, for all practical purposes, to only a very few laboratories that have chosen, for commercial purposes, to market their assay as a "single test". We recommend that these criteria be revised to focus on the content in the NCCN guidelines but at the same time acknowledge the growing collection of high-impact publications regarding molecular testing in metastatic colon cancer.

The policy states the following:

CGP analysis using multiplex or next generation sequencing technology is reasonable and necessary to guide targeted and/or immune-oncology patients with metastatic colorectal cancer when ALL of the following criteria are met.

AMP and CAP recommend that the words "ALL of" be struck from this sentence.

We have further recommendations for revisions to the ten specific testing criteria outlined in the draft LCD. In particular, we recommend:

Criterion Four:
"The CGP is a hybrid-capture based NGS platform that can detect all four types of DNA alterations seen in cancer – base pair substitutions, small indels, copy number alterations and rearrangements – in hundreds of cancer-related genes with high sensitivity and specificity that has been validated in a peer-reviewed journal(s)"

a) The requirements for an assay that is exclusively "*hybrid capture-based*" should be deleted. Many NGS-based strategies employ amplicon-based library preparation, which are equally effective as hybrid-capture to identify protean and important genomic aberrations (Lih CJ, Sims DJ, et al) (Lih CJ, Harrington, RD, et al). In addition, a large, multi-site clinical trial sponsored by the National Cancer Institute, Molecular Analysis for Therapy Choice (NCI-MATCH), utilizes genomic testing that is amplicon-based, not hybrid-capture based. This testing strategy was thoroughly investigated prior to deployment, and has been successfully utilized to detect many different pathogenic genomic alterations. This non-hybrid capture-based NCI-approved CGP test will be used to screen thousands of tumors for actionable mutations, and this test will be submitted for FDA approval. Thus, the provision in this LCD mandating only a hybrid capture-based NGS methodology does not take into account the current state of the art in laboratory science, and could lead to significantly decreased patient access to testing.

b) The requirements for an assay that detects aberrations in "*hundreds of cancer related genes*" should be deleted. The number of clinically "actionable" genomic gene targets is a matter of considerable scientific debate, and many laboratories offer clinically validated NGS-based testing that targets less than "hundreds"
of genes. Moreover, the number of genes to detect clinically significant and specific therapy response has not been firmly established in tumors with high-mutational burden. More literature is needed prior to mandating "hundreds" of target genes. At this time, we recommend that the requirement be limited to those genes found to be actionable in the current NCCN guidelines, including expanded RAS testing (i.e. KRAS, NRAS), BRAF, MSI and may also potentially include other emerging biomarkers such as HER2 amplification, CMET amplification, and/or TMB.

c) The requirement for an assay that has been "validated in a peer-reviewed journal" should be deleted. We are unaware of any precedent in the history of CMS laboratory medicine coverage policy that any assay be "validated in a peer-reviewed journal". Many extensively validated CGP assays are developed in non-academic reference laboratories whose commercial mission often does not prioritize publication in a peer-reviewed medical journal. Even FDA does not mandate publication of assay validation details in a peer-reviewed journal.

Criterion Five
"The laboratory providing CGP testing services must meet the minimum requirements of being CLIA-certified, CAP-accredited and approved by the New York State Department of Health…"

The New York State Department of Health's (NYSDOH) requires premarket review by Clinical Laboratory Evaluation Program (CLEP) if the test is performed in New York State or the sample is from New York State. The WPS Jurisdictions are J5 and J8. Laboratories within the WPS jurisdictions do not test patient samples from New York state unless they have a large outreach business serving patients in New York. In the State of New York, CLEP compliance supersedes other forms of accreditation to avoid duplicative requirements, but this does not apply to labs in the WPS jurisdictions that would require multiple rounds of certification. The "New York State" requirement would place an unnecessary financial and regulatory burden on laboratories that serve only a local patient population. Furthermore, 2018 NCCN guidelines for colorectal cancer state testing should be performed only in CLIA-approved laboratories and make no mention of New York State premarket review. As such, this criterion will act as an impediment to laboratory adoption of CGP assays and is likely to reduce local cancer patient's access to this testing.

We recommend that WPS strike the requirement for New York State Department of Health approval.

Since the MolDx program's policies are now applied in approximately half the country, AMP and CAP believe it would not only be appropriate, but legally required, that testing requirements comply with the Department of Health and Human Services' national regulations, rather the requirements of any single state's health department. Specifically, we recommend the requirement be altered to state that the laboratory be "CLIA-

certified or equivalent, as required." The draft policy requirement, as written, implies that all laboratories – whether or not they provide services to patients in the state of New York - must be certified by the New York State Department of Health in order to perform CGP testing in colorectal cancer patients.

Criterion Eight

WPS requires the following: *Testing is performed with an assay that has been reviewed via the MolDx Technical Assessment process and is listed as a "Covered Test" on the MolDx website.*

AMP and the CAP continue to disagree that the MolDX technical assessment requirement is necessary to review the analytic validity of each LDT or modified IVD. In order to be reimbursed by Medicare, the laboratory must be CLIA certified. CMS has already certified the laboratory (and all the tests it performs) under the CLIA program, which sets a standard for quality control for all tests performed. Analytical validity is thus already substantively addressed by CLIA regulations, which require laboratories to demonstrate analytical validity and regular proficiency testing. Assuring clinical validity is not directly evaluated by CLIA. In particular, CLIA regulations under 42 CFR § 493.1445(e)(3)(i) require the laboratory director and technical supervisor to ensure that selected test methodologies are capable of providing the quality of results required for patient care. Implicit in this regulation is the responsibility of the laboratory director to use medically relevant test methodologies that have an effective clinical purpose—otherwise those methodologies could not be said to be "required for patient care" (U.S. System
of Oversight of Genetic Testing). Thus, the effective clinical purpose or clinical validity is typically documented by the laboratory in review of medical literature. If a lab is not CLIA certified, the test cannot be paid for by Medicare.

Criterion Nine

WPS proposes requiring the inclusion of an expanded RAS panel, BRAF panel, HER2 amplification, MSI, and TMB in the covered CGP panel. We believe that requiring testing of HER2 amplification is overreaching, and requiring TMB should be further established by peer-reviewed literature before being included as a requirement. For example, NCCN colon cancer guidelines (version 2.2018), which MolDX has traditionally considered "gold standard" for clinical utility coverage determinations for other novel laboratory tests, specifically states that: "Larger confirmatory studies are needed, and the panel does not recommend HER2 testing for prognostication or treatment planning at this time". The same NCCN colon cancer guidelines do not mention any role for tumor mutation burden testing, confirming that, although TMB may be a promising early-stage investigational biomarker in the research setting, the data is not sufficiently mature to mandate that TMB be an absolute requirement for NGS-based CGP testing for colon cancer in the routine clinical care setting. The current 2018 NCCN colon cancer guidelines require RAS, BRAF and MSI genotyping but do not recommend a specific methodology (eg. NGS, sequencing, hybridization).

We, therefore, recommend that the policy be revised as follows: "The panel includes established biomarkers such as expanded RAS testing, BRAF, MSI and may also potentially include other emerging biomarkers such as HER2 amplification, CMET amplification, and/or TMB."

Criterion Ten

We request that this criterion be amended as follows: "Potential referral to an expert in HCRA and other specialists when an alteration may suggest a hereditary cancer syndrome. Such alterations may include but are not limited to the following genes: APC, MYH, MLH1, MSH2, MSH6, PMS2, EPCAM, POLE, POLD1, PTEN, or STK11." The NCCN guidelines acknowledge that while research has demonstrated a potential increased risk for CRC associated with mutations such as POLE and POLD1, the value of including these genes for clinical testing remains uncertain. In an analysis of 858 Spanish patients with early onset and/or familial CRC and/or colonic polyposis, only one patient was found to have a POLE mutation (Valle L, Hernandez-Illan E, Bellido F, et

al). In addition, there are numerous other genes that have been implicated in potentially being involved in hereditary colon cancer syndromes such as BRCA1, BRCA2, and TP53 (Pearlman R, Frankel WL, et al).

CPT Coding

We note that the draft LCD mandates the use of molecular, NOS CPT coding (81479) for submission of claims. This approach is in stark contradiction to previous requirements from MolDx to exclusively utilize the most appropriate existing CPT code. In this case, existing genomic sequencing codes (81445, 81455) appropriately describe the scope

of services proposed in this LCD. Specifically, the existing codes note the inclusion of 'interrogation for sequence variants and copy number variants or rearrangements, if performed'. All classes of alterations described in this LCD are included in this CPT descriptor. Tumor mutation burden and MSI, when performed as part of a next generation sequencing based assay, are bioinformatic derivatives of single nucleotide alterations and insertion/deletion alterations. For instance, MSI testing commonly relies on the analysis detection of insertion/deletions in 5 genes (KIT [BAT-25], MSH2 [BAT-26], SLC7A8 [NR-21], ZNF-2 [NR-24], MAP4K3 [MONO-27]
either by fragment analysis (Bacher JW et al. 2004) or by NGS sequencing (Hempelmann JA et al. 2015) . Thus, it would be inappropriate for WPS to require a non- specific "not otherwise specified" CPT code, given the existence of a specific CPT code which appropriately describes the scope of services. A precedent also exists in previously finalized LCDs from National Government Services that used the CPT codes 81445 and 81450 for
Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376) or Acute Myelogenous Leukemia (L36926). **Therefore we recommend the use of CPT codes 81445 and 81455 (rather than 81479) to fulfill criteria for CGP testing, analogous to the LCD from WPS on Non-Small Cell Lung Cancer.**

If an individual laboratory's assay is sufficiently unique such that existing CPT codes do not appropriately apply to the assay, the laboratory should endeavor to have their assay recognized through appropriate channels, which would require obtaining a Proprietary Laboratory Analyses (PLA) code through the American Medical Association's CPT Editorial Panel process, rather than inappropriate utilization of 81479 as suggested in this LCD.

The criteria for CGP can also be fulfilled with additional CPT codes that WPS did not include in its draft policy proposal. For example, **consideration should also be given to other CPT codes that would include PCR-based testing (eg KRAS1 81275, KRAS2 81276, NRAS 81311, BRAF 81210, MSI 81301), FISH, and/or cytogenomic microarrays.** For example, NCCN guidelines V2.2018 state "Testing for MSI *may* be accomplished with a validated NGS panel, especially in patients with metastatic disease who require genotyping of RAS and BRAF. Additionally, a footnote within the same guidelines state "IHC for MMR and DNA analysis for MSI are different assays measuring the same biological effect.

ICD-10 Coding

The proposed policy lists ICD-10 codes, C18.0-C18.9; C19; C20; C78.5; C7a.020-C7A.029; Z85.038; and Z85.048 as the only codes that support medical necessity. Given that the title of this LCD specifies patients with "metastatic colorectal cancer", we do not understand why the draft LCD only contains ICD-10 codes for tumors located within the lower intestinal tract, rather than tumors outside the intestines that represent metastases from an initial primary colorectal tumor that have spread to any of many other anatomic sites. (CMS and NCHS 2017) We contend that there are at least an additional 82 ICD-10 codes that should be included in this proposed metastatic colon cancer policy.

We request that additional ICD-10 codes added to this policy include, but not be limited to the following list:

C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant

C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C21.1	Malignant neoplasm of cloacogenic zone
C21.2	Malignant neoplasm of anal canal
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C72.0	Malignant neoplasm of spinal cord
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C78	Secondary malignant neoplasm of respiratory and digestive organs
C78.0	Secondary malignant neoplasm of lung
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.3	Secondary malignant neoplasm of other and unspecified respiratory organs
C78.30	Secondary malignant neoplasm of unspecified respiratory organ
C78.39	Secondary malignant neoplasm of other respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.8	Secondary malignant neoplasm of other and unspecified digestive organs
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
C79.0	Secondary malignant neoplasm of kidney and renal pelvis
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.1	Secondary malignant neoplasm of bladder and other and unspecified urinary organs
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.3	Secondary malignant neoplasm of brain and cerebral meninges
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.4	Secondary malignant neoplasm of other and unspecified parts of nervous system
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.5	Secondary malignant neoplasm of bone and bone marrow

C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.6	Secondary malignant neoplasm of ovary
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.7	Secondary malignant neoplasm of adrenal gland
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.8	Secondary malignant neoplasm of other specified sites
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
C80	Malignant neoplasm without specification of site
C80.0	Disseminated malignant neoplasm, unspecified
D37	Neoplasm of uncertain behavior of oral cavity and digestive organs
D37.3	Neoplam of uncertain behavior of appendix
D37.4	Neoplasm of uncertain behavior of colon
D37.5	Neoplasm of uncertain behavior of rectum
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
D37.1	Neoplam of uncertain behavior of stomach
D37.2	Neoplam of uncertain behavior of small intestine
D43.0-D43.4	Neoplasm of uncertain behavior of brain & spinal cord
D49	Neoplasms of unspecified behavior
D49.0	Neoplasms of unspecified behavior of digestive system
D49.6	Neoplasm of unsp behavior of brain
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.9	Personal history of malignant neoplasm

We respectfully ask that you consider these comments which were prepared by expert members of AMP and CAP who provide services to Medicare beneficiaries covered by WPS. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever else is needed to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Policy Analyst, 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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