



March 23, 2017

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RE: Comprehensive Genomic Profiling to Guide Treatment in Patients with Advanced Primary Peritoneal, Fallopian Tube and Ovarian Cancer (DL37045)

Dear Dr. Jeter,

Thank you for the opportunity to comment on DL37045. 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.

The Association for Molecular Pathology (AMP) is an international medical and 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 medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

Members of both the CAP and AMP are experts in molecular pathology and the implementation of this coverage policy will directly affect access to testing for Medicare beneficiaries as well as the practice of pathology. We are submitting a joint comment letter because both our organizations have the same views regarding this draft LCD and, as such, we request that Palmetto consider the recommendations outlined in this letter.

We support Palmetto's proposal to cover comprehensive genomic profiling (CGP), which frequently incorporates next generation sequencing (NGS)-based strategies. However, we believe the implementation of this draft policy, as written, will significantly restrict patient access to testing because only a few laboratories can duplicate the overly stringent testing requirements outlined in the draft.

We have found no evidence in the scientific literature that all of the requirements outlined in the draft improve care or outcomes. Limiting coverage to a relatively small number of tests meeting these criteria could ultimately restrict access without a justifiable improvement in patient care and outcomes. Furthermore, we are concerned that leaving genomic testing under the purview of a relatively small number of would potentially create a testing access issue for patients and severely affect clinical care.

Our following comments are supported by the medical literature that will broaden the restrictive testing criteria so that more high-quality, stringently compliant laboratories can also offer this clinically-proven testing to their patients.

Coverage Indications, Limitations, and/or Medical Necessity

dLCD statement: "This policy provides coverage for comprehensive genomic profiling (CGP) on tumor tissue-only for patients diagnosed with advanced primary peritoneal, fallopian tube or ovarian cancer....Unless a patient has signs and symptoms of specific disease, germline (i.e. inherited) testing for genomic alterations by "hotspot" NGS (next generation sequencing), CGP, or any other technology, is not a Medicare benefit."

Comment: It is unclear from this statement if testing is restricted to tumor tissue only or if germline testing may also be performed in the context of tumor-normal pairs to assess true somatic variants. We would recommend that the requirement for not testing matched normal tissue be deleted (but, of course, not covered as a billed procedure) as many labs find this comparative testing to be useful for distinguishing true somatically-acquired tumor-associated variants from benign germline polymorphisms.

The LCD refers to this type of testing as comprehensive genetic profiling (CGP). In these comments, we will instead refer to multiplex or next generation sequencing (NGS) to describe both CGP and what the CPT manual describes as genomic sequencing procedures (GSPs). We believe that aligning the terminology utilized in LCDs to be consistent with the AMA CPT manual is essential to a complete understanding of the LCD.

CGP Test Description

dLCD statement: “CGP analysis is defined as a single test using tumor tissue only (i.e., not matched tumor and normal) that can detect ALL of the following classes of alterations and genomic information in a single test...” The dLCD also states, “Other non-NGS testing platforms may be considered if they can similarly detect all four classes of alterations and this additional genomic information with comparable test performance as CGP...”

Comment: We believe that requiring the detection of all six classes of alterations and genomic information (base pair substitutions, small indels, copy number alterations, rearrangements, tumor mutational burden (TMB), and microsatellite instability (MSI) is overly burdensome to laboratories that use alternative technical approaches to provide the comparable findings, and does little to guide treatment and increase clinical benefit to the patient. Medical necessity must be paramount in any coverage determination and the medical necessity for all six classes of genomic alterations has not been established.

Moreover, there is no medical literature to suggest multiple genomic aberrations need to be detected by a “single test”, as mandated on page four 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.

With specific regard to primary fallopian and ovarian tumors, while there are known recurrent single nucleotide variants and copy number variants, translocations and fusions are less commonly implicated in the oncogenesis of these tumors. Therefore, the clinical value added by requiring the reporting of “rearrangements” is of questionable clinical utility and not supported by current literature or consensus guidelines.

Ovarian cancer is characterized by a high degree of genomic instability (deletions/amplifications) and relatively low mutational burden (except for TP53). There are no known recurrent genomic rearrangements/translocations that are discovered to date. Therefore, clinical utility of testing for translocations/fusions in ovarian cancer will be low; the ability to detect those should not be a required part of the offered assay. (ovary TCGA, 2011 Nature 474, 609–615).⁷

Recommendation: We recommend that Palmetto:

1. NOT require the detection of all 6 classes of genomic alterations. In primary peritoneal, fallopian and ovarian cancer, most common variants are single nucleotide variants (SNV, Particularly in TP53), small indels (particularly in ARID1A) and copy number changes (namely amplifications in MDM2 and MDM4). The role of TMB, MSI and rearrangements remains to be determined.^{1,2}
2. NOT require the detection of all of these alterations in a single assay.
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.

Coverage Summary

dLCD statement: CGP analysis using multiplex or next generation sequencing (NGS) technology is proven to be reasonable and necessary to guide targeted and/or immuno-oncology therapy in patients with advanced ovarian, primary peritoneal, or fallopian tube cancer when **ALL** of the following criteria are met:

Comment: AMP and CAP disagree that all 10 criteria listed in the proposed policy must be met and combined into a “single test” to qualify as medically necessary. These overly stringent criteria will limit CGP testing for primary peritoneal, ovarian and fallopian cancers, for all practical purposes, to a few laboratories that have chosen, for commercial purposes, to market their assay as a “single test”.

Recommendation: AMP and CAP recommend that the words “ALL” be struck from this sentence, and that the criteria be revised to reflect the content in the NCCN guidelines.⁶ If Palmetto declines to strike the word ALL, we offer the following comments and recommendations for revisions to the criteria.

Coverage Criterion

Criterion two: “The patient's tumor has not been tested for genomic alterations via CGP methods”

Comment: The statement in the dLCD is unclear on several points. First, it is not clear whether “not been tested for genomic alterations” refers to any of the molecular pathology series of codes (e.g., TP53 single gene testing), or just the GSP codes. It is also not clear whether the restriction applies to a tumor resected/sampled on same date of service (e.g., multiple tests on the same tumor) or whether this restriction applies to all resections of the tumor including relapse after treatment failure or metastasis. There may be utility in testing in either scenario. In the former case, a negative test by a smaller panel or single gene test might require the use of GSP for a more comprehensive profile. In the latter case of recurrence or metastasis, clonal evolution and tumor development of resistance mutations are a likely cause of progression and can be diagnosed via a more comprehensive panel, even when a GSP of the primary tumor has been performed.

Recommendation: We recommend that this statement be removed in its entirety or that it be clarified to include the repeat GSP sequencing of recurrences and metastases as well as expanded sequencing of initially negative cases.

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)”

Comments: (a) CGP reflects a combination of strategies to detect important alterations such as the ones listed above. Many NGS-based strategies employ amplicon based library preparation, which are equally effective as hybrid-capture to identify protean and important genomic aberrations.^{3,4} 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 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.

(c) 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.

Recommendation: (a) The requirement for an assay this is exclusively “hybrid capture-based” should be deleted.

(b) The requirements for an assay that detects aberrations in “hundreds of cancer related genes” should be deleted.

(c) The requirement for an assay that has been “validated in a peer-reviewed journal” should be deleted.

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 for performing the comprehensive genomic profile test”

Comment: 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 Palmetto GBA jurisdiction is South Carolina, Virginia, West Virginia, and North Carolina. Laboratories within the Palmetto GBA jurisdiction 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 Palmetto GBA jurisdiction 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. 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.

Recommendation: We recommend that Palmetto strike the requirement for New York State Department of Health approval. Since the MoIDx 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 require that the lab be “CLIA-certified or equivalent, as required.” This requirement, as written, implies that all laboratories – whether or not they provide services to patients in the state of New York - are required to be certified by the New York State Department of Health to perform CGP testing in advanced primary peritoneal, fallopian tube and ovarian cancer patients.

Criterion seven and eight: “Testing is performed by a lab that satisfies Palmetto GBA’s Analytical Performance Specifications for Comprehensive Genomic Profiling (M00118, v1); and” “Testing is performed with an assay that has been reviewed via the MoIDx Technical Assessment process and is listed as a “Covered Test” on the MoIDx website;”

Comment: AMP and the CAP continue to disagree that Palmetto’s 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: “The panel includes BRCA1, BRCA2, HER2, BRAF, MSI and TMB.”

Comment: Palmetto 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 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 1.2017), which Palmetto has always 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.

Recommendation: We 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: “Potential referral to an expert in hereditary cancer risk assessment and other specialists when a BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, BRIP1, BARD1, RAD51C, or RAD51D alteration is identified to determine if a hereditary cancer syndrome exists.”

Comment: We are in agreement with this list and suggest it be expanded to include other cancer predisposition genes. In a study in 2011 of 360 women with primary ovarian, peritoneal or fallopian tube cancers, loss of function germline variants in 12 genes including MRE11A, NBN, PALB2 and TP53 were reported.⁵ These 4 genes are not listed in your criterion, arguing for a more inclusive and flexible list.

Recommendation: We suggest the statement be expanded as follows to include other cancer genes: “Potential referral to an expert in hereditary cancer risk assessment and other specialists when alterations are identified that could suggest a hereditary cancer syndrome exists (e.g., BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, BRIP1, BARD1, RAD51C, or RAD51D, MRE11A, NBN, PALB2 and TP53).

CPT/HCPCS Codes

Comment: The proposed policy mandates the use of Not Otherwise Specified (NOS) CPT code 81479 for submission of claims. This approach is in stark contradiction to previous requirements from Palmetto MoIDx 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. Thus, it would be inappropriate for Palmetto 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).

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 Palmetto did not include in their draft policy proposal. For example, consideration may also be given to other CPT codes that would include PCR-based testing, FISH, and/or cytogenomic microarrays.

Recommendation: We recommend the use of CPT codes 81445 and 81455 (rather than 81479) to fulfill criteria for CGP testing, analogous to the LCD that Palmetto recently finalized on Non-Small Cell Lung Cancer.

ICD-10 Codes

The proposed policy includes diagnosis codes for patients with advanced primary cancer. Because advanced cancers have usually spread to other parts of the body, the policy should also include diagnosis codes for both primary and secondary neoplasms. For example, when ovarian cancer is diagnosed it frequently involves the viscera of the pelvis and abdomen, so coverage should also apply to secondary neoplasms of these and other sites.

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

- C21.2 Malignant neoplasm of cloacogenic zone
- 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
Z85.9	Personal history of malignant neoplasm, unspecified

We would welcome the opportunity to work with you to devise a revised policy for coverage and reimbursement for CGP testing in patients with advanced primary peritoneal, fallopian tube and ovarian cancer that will grant access to a larger number of patients.

Thank you again for the opportunity to 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.

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