



COLLEGE of AMERICAN PATHOLOGISTS

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Tamara Syrek Jensen, J.D.
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

Dear Ms. Jensen,

Thank you for the opportunity to review and comment on CMS' proposed national coverage determination (NCD) entitled "*Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)*." 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, patient-facing healthcare providers, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

Members of the CAP are experts in molecular pathology, and the CAP appreciates CMS' effort to provide national coverage for precision medicine offered by next generation sequencing. However, the CAP is concerned that the proposed NCD constitutes an anomalous attempt to specify the medically reasonable and necessary clinical utilization of an entire family of methodologies ("Next Generation Sequencing"), rather than more appropriately addressing the detection of specific genetic mutations that are clinically relevant. The implementation of the proposed NCD criteria would have profound adverse and immediate consequences for access to therapies by Medicare beneficiaries, and treating physician's ability to order medically necessary tests. Future development of test-based cancer therapies would also be impacted.

First and foremost, next generation sequencing is not a diagnostic test for which a NCD can reasonably be promulgated, but an extremely general family of laboratory methodologies.

The medically reasonable and necessary applications of NGS vary by patient condition, and established usage is evolving rapidly. With regard to detecting acquired mutations in specific cancer genes, NGS methodologies are often used in "gene panel" tests that simultaneously sequence multiple "actionable" genes that can be the target of precision medicine drugs of direct therapeutic (and in some instances diagnostic) relevance to particular cancer sub-types. NGS methodologies thus facilitate the simultaneous sequencing of multiple genes of relevance to a cancer sub-type in a single, efficient, cost-effective and specimen-conserving process.

The appropriate diagnostic lab test to be assessed for clinical utility by CMS should be the target gene or genes being interrogated for mutations. The presence or absence of mutations in such specific genes, not the methodology used to detect their alterations, is what determines the sensitivity of a patient's tumor to targeted cancer therapies.

All previous Medicare coverage decisions related to detecting cancer gene mutations that may predict responses to targeted therapies have been applied appropriately to diagnostic testing, irrespective of methodology, for detection of mutations in specific subsets of genes and cancers. These coverage decisions quite appropriately apply to all instances of a test that will detect these targetable mutations for precision oncology, irrespective of methodology. This proposed NCD constitutes a misguided attempt to determine clinical utility of an entire family of methodologies,



rather than appropriately to provide coverage for the detection of the specific genetic mutations that are clinically relevant.

Moreover, upon urging of both governmental and private payers, the American Medical Association (AMA) has moved to develop molecular pathology Current Procedural Terminology (CPT) codes that are method agnostic, focusing on identifying specific genetic analytes and disease/syndrome-specific testing¹. Creating a NCD that addresses NGS methodologies rather than specific tests jeopardizes efforts to meaningfully codify clinically valid tests, including those that use NGS methods.

CMS proposes non-coverage of NGS as a diagnostic laboratory test when patients and tests do not meet the criteria outlined in the proposed NCD. However, the definition of the service provided in this proposed NCD is inconsistent with both the existing CPT codes designed to describe such services and the philosophy of CPT surrounding molecular testing in general, and multiplexed multianalyte assays in particular. The current construct of molecular pathology CPT codes has strongly advocated being analyte specific and “method agnostic” (i.e. codes should not refer to specific analytical methodologies) in order to accurately describe the analytical services provided, while encouraging development and adoption of the most clinically effective and cost-efficient testing.

The preamble to the *Genomic sequencing procedures (GSP)* section of *CPT 2018*¹ states:

*“Genomic sequencing procedures (GSPs) and other molecular multianalyte assays GSPs are DNA or RNA sequence analysis methods that simultaneously assay multiple genes or genetic regions relevant to a clinical situation. They may target specific combinations of genes or genetic material, or assay the exome or genome. The technology used for genomic sequencing is commonly referred to as next generation sequencing (NGS) or massively parallel sequencing (MPS). GSPs are performed on nucleic acids from germline or neoplastic samples. Examples of applications include aneuploidy analysis of cell-free circulating fetal DNA, gene panels for somatic alterations in neoplasms, and sequence analysis of the exome or genome to determine the cause of developmental delay. The exome and genome procedures are designed to evaluate the genetic material in totality or near totality. Although commonly used to identify sequence (base) changes, they can also be used to identify copy number, structural changes, and abnormal zygosity patterns.....The analyses listed below represent groups of genes that are often performed by GSPs; however, the analyses may also be performed by other molecular techniques (polymerase chain reaction [PCR] methods and microarrays). **These codes should be used when the components of the descriptor(s) are fulfilled regardless of the technique used to provide the analysis, unless specifically noted in the code descriptor.** [Bold type added for emphasis].....The assays in this section represent discrete genetic values, properties, or characteristics in which the measurement or analysis of each analyte is potentially of independent medical significance or useful in medical management.”*

It is immediately apparent that the services described by the GSP codes cannot be equated with “NGS tests” since they are not performed exclusively using NGS methodologies. Furthermore, the spectrum of clinical scenarios addressed by the GSP-described services exceeds that described in this proposed NCD (e.g. prenatal testing for genetic abnormalities or inherited predisposition to malignancy). Categorical non-coverage of NGS as a diagnostic laboratory test when patients and tests do not meet the criteria outlined in the proposed NCD will be problematic when these services are performed and reported using the available GSP codes. It is critical for CMS to understand and correctly apply the established HIPAA-required coding structure in developing coverage determinations as it has in the past. This departure from that practice in the proposed NCD



jeopardizes the entire system of coding for these services and would require creation of an expensive, time-consuming, unfamiliar, and unnecessary new coding system.

A particularly notable element in the GSP preamble is the statement:

“The assays in this section represent discrete genetic values, properties, or characteristics in which the measurement or analysis of each analyte is potentially of independent medical significance or useful in medical management.”

This statement reflects the AMA’s consistent efforts to codify in CPT specific testing services as specifically as possible as regards the results of the analysis, whether described as individual analytes or as elements of well-defined test panels. It is important to recognize that novel technologies, such as NGS, make it feasible to include in test panels many analytes of variable clinical value and utility. We encourage caution in attempting to codify, and develop coverage policies, for such services by linking them to established testing services (i.e., companion diagnostic tests), which in most circumstances are performed as single analytes. To do so results not only in a sub-optimal evaluation of the NGS-based tests, such as the one specifically addressed by this proposed NCD, but also creates a highly disruptive environment for the performance of other molecular pathology services and the CPT codes used to describe them.

The CAP supports coverage of actual tests, which identify particular analytes or mutations that have clinically demonstrable utility, and has no wish to impede access to Foundation Medicine, Inc’s test. However, we are opposed to the conflation that all diagnostic services using NGS-based technologies are in any sense “a test” for purposes of determining clinical utility, or that they are in any way equivalent as “tests”. The proposed NCD would have the effect of arbitrarily excluding providers from using this entire family of genomic sequencing procedures because of loss of coverage.

The proposed NCD raises several issues that are well beyond the scope of traditional NCDs.

The coverage limitations outlined in the proposed NCD are unprecedented. CMS is attempting to establish conditions of coverage for an entire family of methodologies, which is a significant departure from the statutory requirements for Medicare to cover reasonable and necessary items or services based on existing evidence.

It is well established that clinical validity and analytic validity are two routine and required processes that must be assessed and confirmed in any CLIA-accredited laboratory. To limit coverage to only those specific panels that are FDA-approved or cleared will deny many patients access to these high-quality lifesaving tests.

CMS should rewrite the policy to explicitly define payment criteria for the specific test (i.e., FoundationOne F1CDx test) which was the only test reviewed under the FDA-CMS parallel review process. CMS should not attempt to generalize the NCD as a coverage determination for other test panels based on use of a shared methodology, many of which target a completely different set of cancer sub-types and/or genetic mutations than the Foundation Medicine, Inc., test. Specific genes and/or mutations in certain cancer sub-types are the appropriate testing target for regulatory oversight – certainly not the entire class of diagnostic tools that utilize related methodologies.

Additionally, not all actionable mutations require an extensive or costly NGS panel. This policy will undoubtedly restrict beneficiary access to the care that their treating physician feels is most appropriate. Allowing the treating physician to assess the results of a test that is not in an FDA-approved/cleared panel is strictly analogous to appropriate off-label prescribing of FDA-approved



pharmaceuticals. Clinicians should be allowed to use testing that they feel they understand well enough to choose and apply in the clinical care of their patients. Restricting testing in a fashion more rigorous than the actual therapeutics that testing will guide represents an unreasonable interference in the practice of medicine.

A precedent for Medicare coverage of NGS assays already exists through local coverage determinations (LCDs). Medicare Administrative Contractors (MACs) have developed LCDs that provide coverage for the treatment of non-small cell lung cancer, acute myelogenous leukemia, and myelodysplastic syndromes.^{2,3,4} These LCDs, which were developed using traditional local coverage development processes, define reasonable and necessary criteria, are solidly evidence-based policies supported by multiple professional practice guidelines, and were written with substantial input from recognized professionals in multiple institutions.

The coverage with evidence development (CED) criteria that the proposed policy prescribes will restrict use by most providers. It is not practical to require labs to submit patient information to a registry because of the limitations laboratories face in accessing patient records. Registries should focus on evaluation of information of test results and not on the type of methodology.

In summary, the CAP strongly recommends that the policy be rewritten to explicitly define payment criteria for the FoundationOne F1CDx test, rather than generalized as a global coverage determination for other gene panel tests that happen to use NGS methodologies similar to that of the Foundation Medicine, Inc., test.

Thank you again for the opportunity to comment on this proposed NCD. The CAP welcomes the opportunity to work with CMS to address these important issues that affect the medical care of beneficiaries. Please direct questions to: Nonda Wilson (202) 354-7116 or nwilson@cap.org.

REFERENCES

1. American Medical Association. *CPT 2018: Standard Edition*. Chicago: American Medical Association; 2017.
2. U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services. Genomic Sequence Analysis Panels in the Treatment of Non-Small Cell Lung Cancer (L36376). Local Coverage Determinations (LCD) Index. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36376&ver=3> Updated February, 3, 2016. Accessed December 27, 2017.
3. U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services. Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (DL36926). Local Coverage Determinations (LCD) Index. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=36376&ver=3> Updated December 8, 2016. Accessed December 27, 2017.
4. U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services. Genomic Sequence Analysis Panels in the Treatment of Myelodysplastic Syndromes (MDS) (L37078). Local Coverage Determinations (LCD) Index. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37078&ver=4> Updated October 5, 2017. Accessed December 27, 2017.