American
Clinical Laboratory
Association

January 17, 2018

Ms. Tamara Syrek Jensen
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
Mail Stop #S3-02-01
7500 Security Boulevard
Baltimore, Maryland 21244

Dear Ms. Jensen,

Please accept these comments from the American Clinical Laboratory Association (ACLA) on the proposed decision memo titled "Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)" (Proposed NCD). ACLA is the leading trade association representing clinical laboratories throughout the country, including national, regional, and local laboratories that provide testing for Medicare beneficiaries every day. ACLA member companies have a direct stake in ensuring that laboratory testing that uses NGS technology is available when a Medicare beneficiary's physician determines that it is medically necessary for treatment of the beneficiary.

ACLA supports Foundation Medicine's original request for an NCD for comprehensive genomic profile testing for the management of cancer in patients with solid tumors that are metastatic, including Stage IV and recurrent tumors, with FoundationOne CDx™ (F1CDx). To that end, should CMS limit the NCD to Foundation Medicine's original request as ACLA And other stakeholders recommend, the title of the NCD would need to be modified to reflect limiting the decision to this narrow, product-specific scope: the F1CDx test. However, if CMS extends the scope of the Proposed NCD beyond positive coverage of the F1CDx test, the NCD must be re-characterized and limited to tumor-based somatic multigene NGS oncology panels, because the evidence that CMS cites in the body of the Proposed NCD is limited to such panels. As proposed, the scope of the NCD would reach far beyond the evidentiary support for it. If CMS elects to limit the NCD to tumor-based somatic multigene NGS oncology panels (consistent with the evidence the agency reviewed), the process and final NCD would benefit from CMS opening up a separate NCD to address this category of tests to allow more time for engagement with stakeholders.

ACLA is deeply concerned that the real-world effect of the NCD, were it to be finalized, would be a *de facto* requirement that each laboratory test using NGS technology would need to be approved or cleared as a medical device by the U.S. Food and Drug Administration (FDA) before it is covered by Medicare. The fact that the FDA has not reviewed and opined on the validity of a laboratory test using NGS technology does not mean that evidence of the test's scientific validity is non-existent. Most tests using NGS technology are laboratory-developed tests (LDTs), and there are multiple ways that laboratories show evidence of an LDT's scientific validity, other than submitting the test to the FDA for review. Application of FDA's current medical device review process to LDTs would impede innovation in tests using NGS technology. Whatever the eventual scope of the NCD, CMS must allow Medicare coverage for tests using NGS technology that are validated in ways other than through FDA medical device review.

Despite the extension of the comment period, stakeholders have not had adequate time to review and understand the full implications of what would be non-coverage for all but a small handful of laboratory tests that use NGS technology – an important factor in the acceleration of personalized medicine. Finalizing the NCD as proposed effectively would "slam on the brakes" with respect to advances that have allowed clinicians to tailor medical treatment to the individual characteristics of each patient. If CMS were to proceed with finalizing an NCD for laboratory testing that uses NGS technology that is broader than Foundation Medicine's initial request, ACLA urges the agency to do so only after the agency has consulted with the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), the Clinical Laboratory Improvement Advisory Committee (CLIAC), as clinical experts who develop and use laboratory testing using NGS technology, laboratorians, patients, and other stakeholders.

ACLA objects to several aspects of the Proposed NCD, as drafted. The Proposed Decision (Section I) is inconsistent in some respects with statements made in the background section and the sections on the history of Medicare coverage, general methodological principles, evidence, and CMS analysis. Furthermore, we find it problematic that the Proposed NCD would base coverage or non-coverage on the technology used to perform the test, rather than on the purpose of the test, as other NCDs do. These issues deserve more study and discussion between CMS and various stakeholders before the agency proceeds with an NCD involving NGS testing beyond tumor-based somatic multigene NGS oncology panels.

A. Background on Next Generation Sequencing

Next Generation Sequencing refers to a technology platform whereby an entire human genome – or specific areas of interest – can be sequenced rapidly to detect deletions of DNA, large genomic deletions of exons or whole genes, and rearrangements in genes. An NGS platform can sequence millions of small fragments of DNA simultaneously. Bioinformatics analyses are used to synthesize the fragments by mapping the individual reads to the human reference genome. Simply put, NGS is not a class of tests – it is a methodology that is used with a laboratory process to answer specific questions to aid in management of a patient's disease.

NGS has not entirely taken the place of traditional Sanger sequencing, but it is far faster, can be more cost-efficient, allows for simultaneous interrogation of the entire genome, and can be used with samples with low-input DNA. Instead of sequencing a single DNA fragment, an NGS platform extends this process across millions of fragments in parallel. Sanger sequencing may require additional assays to be performed (*e.g.*, fluorescence *in situ* hybridization (FISH)) to identify mutations beyond the region of interest, whereas NGS can yield the full spectrum of genomic variation in a single run. Sanger sequencing depends on knowledge of the gene or region under investigation, but NGS is unselective and can identify novel mutations and disease-causing genes.

Laboratory testing using NGS technology has applications in the management and treatment of patients with immunodeficiencies, infectious diseases, cancer, and cardiomyopathies. While most samples are derived from solid tissue, NGS can be performed on liquid specimens, as

well, and the benefits of non-invasive specimen collection will accelerate the development of non-solid tissue NGS applications.

Laboratories use NGS platforms with analytically and clinically-validated LDTs and with commercially-available kits that are cleared or approved by the FDA. In many cases, LDTs yield better and more up-to-date results than FDA-approved kits. A recent peer-reviewed study published in the journal Molecular Diagnosis & Therapy assessed mutations detected in *EGFR*, *KRAS*, and *BRAF* genes using an LDT that combines NGS with confirmation by Sanger sequencing and compared it with mutations that could be detected by FDA-cleared test kits. The study found that significantly more mutations in these genes are detected when the LDT combining NGS and Sanger sequencing was used than when FDA-cleared kits were used. The study's authors stated that rapid advances in analyzing molecular abnormalities make it difficult for FDA-approved test kits to keep pace and remain the standard in patient care and oftentimes, FDA-approved tests become outdated quickly.[1] Another study, published in JAMA Oncology in December 2017, compared performance of LDTs and FDA-approved assays for *EGFR*, *KRAS*, and *BRAF* testing. The study included 6,897 College of American Pathologists (CAP) proficiency testing responses and found 97 percent accuracy across both FDA-approved assays and LDTs. Authors also noted that more than 60 percent of study participants using FDA-approved assays modified the approved assays to broaden clinical practice, rendering them LDTs.[2]

Testing using NGS technology most often is ordered by a treating physician,[3] but a pathologist also may order such testing. This may be the case, for instance, when a pathologist has examined a tissue specimen and determined that a patient has cancer; the pathologist may consult with the treating oncologist and suggest use of testing using NGS technology to identify molecular abnormalities, and the pathologist may be the physician to place the order. The collaborative approach does not remove the treating physician from management of the patient's condition, but rather involves a pathologist with expertise in laboratory testing using NGS technology in that management.

Sometimes it may be necessary to perform the same laboratory test using NGS technology more than once on the same patient, or it may be necessary for a patient to have a different NGS test, in order for a treating clinician to determine an appropriate course of treatment. Cancer is a heterogeneous and dynamic disease that may be characterized by multiple sub-clones existing in the same tumor or across disease sites. Mutations also may evolve through incomplete DNA replication or as a result of treatment. For example, *EGFR* mutations in exon 20 or T790M have been shown to develop after *EGFR* inhibitor therapy, and mutations in HER2 may evolve after

[1] Mol. Diagn Ther (2017) 21:571-579 (published online June 21, 2017).
[2] Kim AS, Bartley AN, Bridge JA, et al. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. JAMA oncology. 2017.
[3] In the Medicare context for purposes of diagnostic testing, the "treating physician" is a physician, as defined in §1861(r) of the Social Security Act, who furnishes a consultation or treats a beneficiary for a specific medical problem, and who uses the results of a diagnostic test in the management of the beneficiary's specific medical problem. Medicare Benefit Policy Manual, Pub. No. 100-02, Ch. 15, Sec. 80.6.1.

anti-HER2 therapy.[4] Repeat testing after therapy and sampling of tumor tissue from different disease sites should be covered by CMS. This would allow physicians to evaluate treatment response, identify potential new actionable mutations in the current tumor environment, and in the case of sampling from a different disease site, identify actionable mutations that did not exist in the "primary" tumor.

B. The scope of the NCD should be limited to tumor-based somatic multigene NGS oncology panels.

Foundation Medicine's November 17, 2017 letter requested initiation of a national coverage analysis for comprehensive genomic profile testing with F1CDx in patients with metastatic cancers and who are seeking treatment for one of 10 tumor types: bladder, breast, colon, carcinoma of unknown primary (CUP), colon/rectum, endometrial, NSC lung, melanoma, ovary, pancreas, and stomach/gastric.[5] However, the Proposed NCD has a far broader scope than the scope of the request and of the evidence CMS cites in Section VII of the Proposed NCD. The evidence CMS cites to address health outcomes in Medicare beneficiaries focuses almost exclusively on tumor-based multigene panels, yet we understand that the scope of non-coverage in the Proposed NCD would reach <u>any</u> test using NGS technology that does not meet certain criteria. Until and unless CMS reviews evidence relevant to other kinds of laboratory tests using NGS technology, it is inappropriate for the agency to issue an NCD that extends beyond tumor-based somatic multigene NGS oncology panels. CMS should change the title and scope of the NCD accordingly.

C. CMS should not proceed with finalizing an NCD relevant to other types of testing using NGS technology until it has had adequate time to consult with qualified clinical experts, laboratories developing and performing tests using NGS technology, and patient advocacy groups.

ACLA appreciates that CMS recognized that the initial 30 day comment period was inadequate for a proposal with such a potentially large impact on treatment for Medicare beneficiaries and that it extended the comment period. But the longer comment period still has not been adequate for ACLA and other stakeholders to fully vet and respond to the Proposed NCD (especially given the holidays in the middle of the comment period). If CMS believes that it would be appropriate to develop an NCD regarding coverage for testing using NGS technology, it should do so only after adequate consultation with the clinical and laboratory experts who develop and use the technology, not beforehand. Many of the questions CMS asks in the Proposed NCD are conceptually complex and cannot be answered without more time and effort than is allowed in the short comment period – even one that has been extended.

CMS states that it did not consult with the MEDCAC about the Proposed NCD, which would have given stakeholders an additional opportunity to communicate their viewpoints to CMS and to the Committee. CMS notifies stakeholders two months in advance of a MEDCAC meeting

[4] Dagogo-Jack, Ibiayi & T. Shaw, Alice. (2017). Tumor heterogeneity and resistance to cancer therapies. Nature Reviews Clinical Oncology.10.1038/nrclinonc.2017.166.
[5] https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id290.pdf.

about the topics to be discussed and how a member of the public can participate and present information to the committee. CMS's own guidance states that it refers issues to the MEDCAC "when presentation, public discussion, and clarification of the appropriate scope for the technical review, a preferred methodological approach, or a clinical management issue would benefit future NCDs," when "dissemination of a technology may have a major impact on the Medicare program, the Medicare population, or the clinical care for specific beneficiary groups," or when "obtaining the perspective of affected patients and caregivers (*e.g.*, the degree of perceived benefit, subjective assessment of risk, or burden of side effects) through public comments and voting representation on the panel may be relevant."[6] Use of NGS testing for Medicare beneficiaries meet these criteria, and the agency should have taken the time to consult with the MEDCAC on the issues included in the Proposed NCD. The fact that MEDCAC meets only a few times each year is not a sufficient reason to withhold a Proposed NCD from MEDCAC consultation if a topic is appropriate for presentation before the committee, as this is.

We are not aware that CMS "consulted with appropriate outside clinical experts," which is required under statute when CMS does not consult with MEDCAC.[7] CMS also said it "did not request an external Technology Assessment on this issue." It does not appear that CMS consulted with CLIAC, whose charter includes giving advice and guidance to HHS on general issues related to improvement in clinical laboratory quality and laboratory medicine practice and on specific questions related to possible revision in CLIA standards.[8] The laboratory experience and expertise of CLIAC's membership would add immeasurably to CMS's decision-making process. As it stands, CMS risks developing a far-reaching NCD without adhering to procedural requirements included in the statute and without the benefit of expert input from the laboratories and clinicians that work on the cutting edge of NGS testing and technology. For these reasons and others, the scope of the NCD should be no broader than tumor-based somatic multigene NGS oncology panels.

D. If CMS were to proceed with finalizing some version of the Proposed NCD, it first must address its deficiencies.

We believe that finalization of the Proposed NCD with its overbroad scope would hamper the development of innovative testing using NGS technology and would deprive Medicare beneficiaries of currently-available laboratory tests. Nevertheless, if CMS proceeds to finalize some version of the Proposed NCD, we urge the agency to address a number of serious issues presented the draft.

1. Laboratory Developed Tests using NGS Technology

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[6] Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee, *available at* https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=10.

[7] 42 U.S.C. § 1395y(l)(4) ("With respect to a request for a national coverage determination for which there is not a review by the Medicare Coverage Advisory Committee, the Secretary shall consult with appropriate outside clinical experts.").

[8] CLIAC Charter (effective Feb. 19, 2016), *available at*: https://wwwn.cdc.gov/cliac/Charter.aspx.

CMS cannot finalize an NCD regarding testing using NGS technology without recognizing the scientific validity and value of LDTs that are currently available and that currently provide actionable information to physicians treating Medicare beneficiaries. ACLA takes issue with the agency's insinuation in the Proposed NCD that only FDA-cleared or –approved tests are fully validated and that a test using NGS technology that is an LDT cannot "provide assurance to treating physicians and patients that the test is scientifically valid before they rely on the results for selection of cancer treatment." The fact that the FDA has not reviewed and opined on the validity of an LDT does not mean that evidence of its scientific validity is non-existent. ACLA maintains its long-held view that LDTs are not "in vitro diagnostics" or "medical devices", as defined in the Federal Food, Drug, and Cosmetic Act and its implementing regulations, and therefore are outside of the scope of the FDA's current regulatory authority.

Laboratory-developed tests are diagnostic services that are developed, validated, and performed by highly-trained professionals within a single clinical laboratory entity. Physicians routinely depend on LDTs to make crucial medical decisions about the best course of treatment for their patients. Laboratories that provide LDTs are subject to comprehensive regulation by CMS itself, by state regulators, and in many instances by CAP, the world's largest association comprised exclusively of board-certified pathologists and which accredits thousands of laboratories. Laboratories regulated by CMS under the Clinical Laboratory Improvement Amendments (CLIA)[9] and implementing regulations are required to be CMS-certified, and many are state-licensed, as well. Those certifications and licensure requirements work to ensure that laboratories provide accurate information to physicians using methodologies appropriate for patient care, and that laboratory testing processes are supervised and performed by qualified personnel.

CLIA includes extensive requirements for laboratories to verify or establish a test's analytical performance characteristics before offering it and reporting patient results based on the test. CLIA regulations require that laboratories that use LDTs, that modify FDA-cleared or –approved tests, or that use a test system for which the manufacturer did not provide performance specifications, must establish the following performance characteristics before reporting patient test results: accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals (normal values), and any other performance characteristic required for test performance.[10] CLIA regulations also require a laboratory director to ensure that test methodologies have the capability of providing the quality of results required for patient care, which is the case only when they are clinical relevant for the patient populations being tested (*i.e.*, are clinically valid).[11] Clinical validity also is ensured by accreditation by an approved third-party accreditation organization such as CAP, whose goals include ensuring that tests are analytically and clinically valid, that there is patient safety and

[9] 42 U.S.C. § 263a *et seq.*
[10] 42 C.F.R. § 493.1253(b)(2).
[11] 42 C.F.R. § 493.1445(e)(3)(1).

patient access to testing, and that there is innovation and improvement of LDTs.[12] Currently, approximately 8,000 laboratories are CAP-accredited.[13]

Precisely because LDTs are not required to undergo premarket FDA-clearance or -approval as devices, laboratories are able to innovate and improve their services rapidly and continually. Laboratories thus have the flexibility and technical expertise to adapt in real time to the latest scientific advances in NGS technology. Laboratory tests using NGS technology can be modified and improved rapidly, and indications for use may be expanded without altering any test processes or analytic standards. Yet under the FDA's current medical device review paradigm, many innovative modifications would require additional FDA review before use, which would add considerable unnecessary time and costs to the process, without evidence that the additional time provides higher quality testing or better patient care. Moreover, we are concerned that the FDA does not have the resources it needs to conduct reviews on the submissions it receives currently for laboratory tests, let alone all laboratory tests using NGS technology. Effectively restricting Medicare coverage to FDA-cleared or –approved tests not only would deprive Medicare beneficiaries and their physicians of the most advanced diagnostic information available—in many cases, where no FDA-cleared or –approved test exists, Medicare beneficiaries and their physicians would be deprived of actionable diagnostic information altogether.

In the list of questions for commenters to address in the Proposed NCD, CMS acknowledges that laboratories may use various methods to assess the analytical and clinical validity of tests, other than waiting for the FDA to determine the scientific validity of a test. One such approach involves pre-market review and approval by the New York State Department of Health (NYSDOH) of LDTs offered to New York State residents. NYSDOH reviews LDTs for both analytical and clinical validity, and according to SACGHS, an estimated 75 percent of the genetic tests offered in the United States are subject to New York State oversight.[14] The FDA recently recognized the value of NYSDOH oversight by designating it as an approved third-party reviewer of certain FDA regulatory submissions and by accepting certain submissions to the NYSDOH to inform FDA's decisions. Another approach is for CMS to continue to rely on Medicare Administrative Contractors' (MACs') assessment of whether a laboratory test using NGS technology should be covered by Medicare, given its analytical and clinical validity and clinical utility. The MACs invest tremendous time and effort learning about test methodology and usage before issuing a positive Local Coverage Determination (LCD), and this avenue should remain available to laboratories seeking coverage of a test using NGS technology.

2. Coverage with Evidence Development unnecessarily restricts Medicare beneficiary access to valuable testing.

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[12] Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services (Apr. 2008).
[13] College of American Pathologists 2016 Annual Report, *available at* http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cap-annual-report.pdf.
[14] SACGHS at 36-37.

While the Proposed NCD appears to allow for Coverage with Evidence Development (CED) of certain LDTs using NGS technology that are provided to patients as diagnostic tests within the NIH-NCI National Clinical Trial Network clinical trials and that are registered in the NIH Genetic Testing Registry, this provision is unnecessarily restrictive. ACLA has shared its concerns with CMS in the past about CED, and our concerns have not been allayed by the Proposed NCD. CMS's CED research may collect new evidence in the long-run, but restricting coverage for Medicare beneficiaries outside of CED clinical trials is short-sighted.

In contrast to the typically direct relationship between a therapy and health outcomes, the relationship between a laboratory test and a health outcome usually is indirect or is very difficult to ascertain in a reasonable period of time with traditional trial designs. The appropriate standard for a clinical laboratory tests is not necessarily tied to a patient outcome – this does not yield useful information about the analytical or clinical validity of a test. It is rare (and impractical) for a laboratory to conduct prospective randomized clinical trials to show that a molecular test has clinical utility; this usually can be deduced from other available evidence about changes in physician behavior without the considerable time and expense inherent in clinical trials. Coverage of new tests could be delayed by years if CMS accepts only published studies from peer-reviewed journals of prospective randomized clinical trials, or, in the absence of such studies, refuse to accept other evidence of clinical utility.

For laboratories, CED is unworkable and inappropriate as proposed. Many laboratories do not have the resources to participate in NIH-NCI clinical trials. And laboratories oftentimes do not have access to data that are required by a registry, such as overall survival, progression-free survival, objective response rate, and patient-reported outcomes. Thus, for many laboratories, the "choice" to use CED for an LDT using NGS technology, in lieu of FDA-approval or –clearance, is not a real choice.

3. Coverage cannot be limited to only those tests that are ordered by the "treating physician.

As we explain above, there are circumstances in which a pathologist may order an NGS test for a Medicare beneficiary, after examining a specimen and consulting with other members of the treatment team. The pathologist is not the "treating physician," as that term is commonly understood in the Medicare context. Therefore, coverage for testing using NGS technology should not be limited to tests ordered only by the treating physician.

E. Conclusion

ACLA supports coverage of FoundationOne CDx™, but we do not believe that CMS should finalize the Proposed NCD as drafted. The time that stakeholders have had to consider the Proposed NCD and respond to it is woefully inadequate, and the agency has failed in its duty to consult with the public, clinical experts, MEDCAC, and CLIAC before issuing the proposal. To the extent that CMS extends this NCD beyond the initial request from Foundation Medicine, the NCD would benefit from a longer period of stakeholder engagement for input on coverage of different kinds of laboratory tests using NGS technology. CMS's restrictive conditions of

coverage for other tests using NGS technology, amounting to blanket non-coverage, would be a severe impediment to development and use of cutting-edge tests using NGS technology for cancer and other indications – especially those tests that are LDTs – and would deny Medicare beneficiaries access to innovative, scientifically valid, and medically necessary testing that has the potential to reduce overall healthcare costs by avoiding therapies that either will not work for or could be harmful to a Medicare beneficiary.

Thank you for your consideration of ACLA's comments.

Sincerely,

Paul Sheives
Vice President, Reimbursement & Regulatory Policy
American Clinical Laboratory Association