November 25, 2019

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

American
Clinical Laboratory
Association

Dear Ms. Syrek Jensen,

The American Clinical Laboratory Association submits these comments on the Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Stage Cancer (CAG-00450R).[1] ACLA is a not-for-profit association representing the nation's leading clinical and anatomic pathology laboratories, including national, regional, specialty, end-stage renal disease, and nursing home laboratories. The clinical laboratory industry is at the forefront of precision medicine, driving diagnostic innovation and contributing more than $100 billion to the nation's economy annually. ACLA member companies have a direct stake in ensuring that laboratory testing using NGS technology is available when a Medicare beneficiary's physician has determined that it is necessary for medical management of the beneficiary.

We appreciate that CMS reopened NCD 90.2 in response to the concerns expressed by ACLA and numerous other stakeholders about its scope and coverage, and we are grateful for the Coverage and Analysis Group's willingness to engage in a collaborative dialogue with ACLA members about this coverage decision. However, we are concerned that CMS's proposed coverage decision would be detrimental to Medicare beneficiaries' access to precision diagnostics to guide cancer treatments. CMS should nationally cover a hereditary breast and ovarian cancer test using NGS technology, whether the test is a laboratory-developed test (LDT) or has been cleared or approved by the Food and Drug Administration (FDA). In the alternative, regardless of the type of cancer, Medicare Administrative Contractors (MACs) should retain discretion to cover a germline test using NGS technology or another technology platform when the test is performed in a CLIA-certified laboratory, the test is ordered by a treating physician, and the patient is seeking treatment and weighing medical management options based on germline mutation status. Additionally, we request that the agency remove overly-broad language in the proposed decision memo on coverage for a test using NGS technology when a beneficiary was "previously tested using NGS." The agency also should revise the broad non-coverage language included in the March 2018 version of the NCD to conform with existing and new text. Our suggestions for changes to the language of the NCD are attached.

A. NGS as a Technology Platform

In the proposed decision memo, CMS refers variously to "NGS as a diagnostic laboratory test" and "NGS testing." NGS alone does not provide a diagnosis, as it is part of the overall testing process that includes data analysis, annotation, and interpretation. NGS is a test methodology for

[1] The name of the NCD should be changed to reflect that coverage of tests using NGS technology is conferred not only for beneficiaries with advanced cancer, but also for beneficiaries with any stage cancer who receive germline testing under certain conditions.

molecular testing, which includes PCR, qPCR, RT-PCR, Sanger sequencing, fluorescence in situ hybridization (FISH), and microarrays. All of these technologies for molecular testing, including NGS, are used in a laboratory process (sometimes interchangeably) to answer specific questions to aid in management of a patient's disease. 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.

NGS has not entirely taken the place of other sequencing methods. However, for many existing covered assays, including tumor gene expression assays, NGS 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 sequencing process across millions of fragments in parallel. PCR-based tests, which are limited by smaller targets, usually require multiple tests to cover all loci of interest to identify relevant variants, whereas NGS-based tests can cover larger regions at comparable costs and with superior accuracy. Laboratories use NGS platforms with analytically- and clinically-validated LDTs and with commercially-available kits that are cleared or approved by the FDA.

B. CMS Should Nationally Cover Hereditary Breast and Ovarian Cancer Tests Using NGS Technology, Whether LDTs or FDA-Cleared or -Approved Tests

ACLA supports national Medicare coverage of germline tests using NGS technology for hereditary breast and ovarian cancer. However, we adamantly oppose CMS's proposal to limit national coverage of these tests to those that are FDA-cleared or -approved. Indeed, there are no such tests on the market today, rendering such coverage illusory. In the proposed decision memo, CMS did not articulate any reason for determining that such a test may be covered by Medicare when it has been FDA-cleared or -approved, but not if it is an LDT or an FDA-cleared or -approved test that has been modified. Naturally, the peer-reviewed studies that CMS cites in support of coverage of hereditary breast and ovarian cancer tests using NGS technology did not involve FDA-cleared or -approved tests—since none exist today.

CMS's own statement supports national coverage of germline testing using NGS technology for hereditary breast and ovarian cancer whether the test is an LDT that is validated in a CLIA-certified laboratory or when it is cleared or approved by the FDA: "For validated tests, we find the benefits in health outcomes of NGS testing for germline mutations for certain cancers outweighs the harms associated with testing."[2] There are multiple ways that laboratories show evidence of an LDT's validity, other than submitting the test to the FDA for review. 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

[2] Proposed Decision Memo, Sec. VIII.

characteristic required for test performance.[3] 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 clinically relevant for the patient populations being tested (*i.e.*, are clinically valid).[4] Clinical validity also is ensured by accreditation by an approved third-party accreditation organization such as the College of American Pathologists, whose goals include ensuring that tests are analytically and clinically valid, that there is patient safety and patient access to testing, and that there is innovation and improvement of LDTs.[5]

A germline test using NGS technology is "validated" when it is performed in a CLIA-certified laboratory, whether the test is an LDT or whether it is an FDA-cleared or -approved test. CMS has provided no evidence to the contrary. It should not finalize its proposal to limit national coverage of hereditary breast and ovarian tests using NGS technology to those that are FDA-cleared or -approved; it should nationally cover tests that are LDTs, as well.

C. MACs Should Retain Discretion to Cover Germline Tests Using NGS Technology

In addition to the discretion afforded the MACs to cover certain tests using NGS technology in beneficiaries with advanced stage cancers, the MACs should retain the discretion to cover germline tests using NGS technology in patients with any type and stage of cancer when certain criteria are met—particularly if the agency does not nationally cover hereditary breast and ovarian cancer tests that are LDTs. Allowing the MACs to develop Local Coverage Determinations (LCDs) for germline testing would accommodate technological advances and changes in evidence-based guidelines that would not require serial changes to the NCD itself.

CMS should allow the MACs to continue to use the existing process for issuing LCDs to cover germline mutation tests using NGS technology that a physician uses in medical management of a Medicare beneficiary. The MACs have well-established methods for consulting with laboratories and other stakeholders, reviewing evidence, and ensuring that tests have been properly validated according to published guidelines (when available), and defining the parameters under which a laboratory test will be covered on a jurisdiction-wide basis. Moreover, retaining broad non-coverage language in the NCD would lead to confusing and illogical coverage inconsistencies, as MACs could continue to cover a test using Sanger sequencing but not NGS technology, and a patient who is commercially insured would have access to a broader array of NGS-based testing options than an otherwise identically situated Medicare beneficiary.

MACs have recognized the value of germline testing and have covered it for some indications for several years. For example, as of 2017, every MAC had an LCD that covers *BRCA1* and *BRCA2* genetic testing for hereditary breast and ovarian cancer, and each was technology-agnostic. In each instance, the patient and the testing had to meet certain criteria to qualify for coverage, but test methodology was not one of the criteria. MAC discretion would maintain beneficiary coverage under such policies, as opposed to the limited proposed NCD language.

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[3] 42 C.F.R. § 493.1253(b)(2).
[4] 42 C.F.R. § 493.1445(e)(3)(1).
[5] 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).

A MAC should be permitted to cover germline testing when:

- The test is performed in a CLIA-certified laboratory;
- The test is ordered by a treating physician;
- The beneficiary is seeking treatment and weighing medical management options based on germline mutation status, as recommended by NCCN guidelines and/or relevant evidence-based medical society guidelines.

These criteria serve to ensure that the testing is covered under a Medicare benefit category and is performed pursuant to national evidence-based medical guidelines, such as those developed by organizations such as the American Society for Clinical Oncology, the College of American Pathologists, the Association for Molecular Pathology, the American Society for Clinical Pathology, the American College of Obstetricians and Gynecologists, and the American College of Medical Genetics, as examples.

D. CMS Should Remove Overly-Broad Language in the NCD on Coverage for a Test Using NGS in a Beneficiary Who Was "Previously Tested Using NGS"

CMS should remove overly-broad language in the NCD on coverage for a test using NGS in a beneficiary who was "previously tested using NGS." Proposed language describing national coverage for hereditary breast and ovarian tests using NGS technology and MAC discretion to cover other germline tests states that the patient must not have "been previously tested using NGS." Yet it is not uncommon for germline-tested patients already to have undergone somatic NGS testing, and different germline tests may cover different sets of genes.

The NCD's language would have the effect of limiting Medicare coverage for medically necessary laboratory testing in a number of circumstances. For example, a treating physician may order a germline test using NGS technology for a beneficiary with early stage breast cancer who previously was tested for colorectal cancer with a test using NGS technology (whether covered by Medicare or not). Even the Palmetto GBA MolDx LCD on Genetic Testing for Lynch Syndrome (the most common hereditary cause of colorectal cancer) adopts a stepwise testing approach, wherein steps four and five include reflexing to germline testing, which the policy considers reasonable and medically necessary.[6] Another example is a beneficiary who has had an NGS-based HIV genotyping test or a red blood cell typing test: under this cancer NCD, either of those tests would be a "previous NGS test", and a later test using NGS technology in that same beneficiary with cancer would not be covered.

It would be nonsensical to non-cover a test for a beneficiary because the test uses the same methodology as an entirely different test the beneficiary had previously. Doing so would be analogous to non-covering a test using Sanger sequencing when the beneficiary previously had

[6] Proposed Local Coverage Determination (LCD): MolDX: Genetic Testing for Lynch Syndrome (L35024), *available at* https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35024&ver=50&SearchType=Advanced&CoverageSelection=Local&ArticleType=BC%7cSAD%7cRTC%7cReg&PolicyType=Both&s=48&KeyWord=Lynch+syndrome&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAAAAA&.

another unrelated test that used Sanger sequencing, or even non-covering a serum potassium test because the methodology (ion selective electrode) is the same as that used for a sodium test.

An issue that has yet to be resolved is coverage for NGS-based tests for minimal residual disease (MRD). Since the issuance of the final Decision Memo and its implementation, additional evidence has been published on the value of tests using NGS technology in the assessment and treatment of patients with cancer. One recent study shows that MRD assessment using NGS technology predicts overall survival and disease-free survival better than flow cytometry or qPCR analysis.[7] The most recent NCCN guidelines for multiple myeloma include response criteria that support the use of tests using NGS technology to identify MRD, and they recommend testing for MRD after each treatment stage.[8] This approach also is discussed in the recommendations of the International Myeloma Working Group.[9] Recent NCCN guidelines for acute lymphoblastic leukemia (ALL) also reference NGS methods for disease assessment in adults at baseline and following different treatment phases.[10]

Repeat testing using NGS technology in patients with multiple myeloma and ALL should not be foreclosed or complicated by language in the existing NCD limiting testing when a patient has been "previously tested using the same NGS test for the same primary diagnosis of cancer," because that is precisely what the evidence-based guidelines call for. Several additional hematologic cancer guidelines also support MRD assessment at relevant points in a patient's cancer care, and it is likely that testing using NGS technology increasingly will be a recommended method for such assessments.[11] CMS should ensure that Medicare beneficiaries with hematologic diseases who may benefit from MRD assessment have access to tests using NGS technology, as recommended by evidence-based guidelines, and the text of the NCD should be clear on this issue.

E. Staging of Hematologic Malignancies

As written, the NCD covers a test using NGS technology in a patient with "recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer." As we have discussed with you in the past, hematologic malignancies are not staged according to a TNM staging system, nor are all hematologic malignancies staged alike. We support the approach to this incongruity that is taken in the Palmetto GBA MolDx draft LCD on Myeloid Malignancies and Suspected Myeloid Malignancies, which classifies these kinds of diseases as refractory and/or metastatic cancers for purposes of Medicare coverage.[12] We have suggested changes to the text of the NCD to reflect that a test using NGS technology may be covered by a MAC when used in a patient with a diagnosis

[7] Onecha E *et al*., A novel deep targeted sequencing method for minimal residual disease monitoring in acute myeloid leukemia. Haematologica. 2019;104(2):288-296.
[8] NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma, Version 2.2019 (Nov. 16, 2019) at MYEL-D 1, 3.
[9] International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-46.
[10] NCCN Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version 2.2019 (May 15, 2019) at ALL-F.
[11] *See, e.g.*, Press, RD *et al.* NGS-defined minimal residual disease before stem cell transplantation predicts acute myeloid leukemia response. Am J Hematol. 2019 May 23. doi:10.1002/ajh.25514.
[12] Proposed Local Coverage Determination: Next Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (DL38047); *available at* https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38046&ver=3&DocID=DL38047&bc=gAAAABAAAAAA&.

with a suspected or diagnosed hematologic malignancy when performed in a CLIA-certified laboratory and ordered by the treating physician.

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Thank you for your consideration of ACLA's comments.

Sincerely,

Julie Khani, President
American Clinical Laboratory Association

Suggested NCD Language

(Additions are in italics; deletions are struck through.)

A. General

Clinical laboratory diagnostic tests can include tests that, for example, predict the risk associated with one or more genetic variations. In addition, in vitro companion diagnostic laboratory tests provide a report of test results of genetic variations and are essential for the safe and effective use of a corresponding therapeutic product. Next Generation Sequencing (NGS) is one technique that can measure one or more genetic variations as a laboratory ~~diagnostic test~~ technology, such as when used as a companion in vitro diagnostic test.

Patients with cancer can have *hereditary*, recurrent, relapsed, refractory, metastatic, and/or advanced stages III or IV of cancer. Clinical studies show that genetic variations in a patient's cancer can, in concert with clinical factors, predict how each individual responds to specific treatments.

In application, a report of results of a diagnostic laboratory test using NGS (i.e., information on the cancer's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad, or none at all. Applications of *tests using* NGS to predict a patient's response to treatment occurs ideally prior to initiation of such treatment.

B. Nationally Covered Indications

Effective for services performed on or after March 16, 2018, the Centers for Medicare & Medicaid Services (CMS) has determined that *a test using* Next Generation Sequencing (NGS) ~~as a diagnostic laboratory test~~ is reasonable and necessary and covered nationally, when performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

1. Patient has:

- either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer, *including any suspected or diagnosed hematologic malignancy*; and,
- either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and,
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:

- Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
- an FDA-approved or -cleared indication for use in that patient's cancer; and,
- results provided to the treating physician for management of the patient using a report template to specify treatment options.

In addition, E~~*e*~~effective for services performed on or after [Month/XX] [Day/XX], [20XX], ~~the CMS, proposes that~~ *CMS has determined that a test using* NGS ~~as a diagnostic laboratory test~~ *is reasonable and necessary and covered nationally* when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

The patient has:

- ovarian or breast cancer;
- clinical indications for germline (inherited) testing, *and*

- risk factors for germline (inherited) breast cancer or ovarian cancer~~; and~~
- ~~not been previously tested using NGS~~.

~~The diagnostic laboratory test using NGS must have all of the following:~~

- ~~FDA approval or clearance;~~
- ~~an FDA approved or cleared indication for use in that patient's cancer; and~~

Results *must be* provided to the treating physician for management of the patient using a report template to specify treatment options.

~~C. Nationally Non-Covered~~

~~Effective for services performed on or after March 16, 2018, NGS as a diagnostic laboratory test for patients with cancer are non-covered if the cancer patient does not meet the criteria noted in section B.1. above.~~

~~D~~. C. Other

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of ~~other~~ *tests other than those described in Section B using* NGS ~~as a diagnostic laboratory test~~ for patients with cancer ~~only~~ when the test is performed in a CLIA-certified laboratory, ordered by a treating physician, and the patient has:

- either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, *including any suspected or diagnosed hematologic malignancy*;
- either not been previously tested using the same NGS-*based* test for the same primary diagnosis of cancer or repeat testing using the same NGS-*based* test was performed only when a new primary cancer diagnosis is made by the treating physician *or to detect minimal residual disease*; and
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

In addition, ~~E~~*e*ffective for services performed on or after [Month/XX] [Day/XX], [20XX], Medicare Administrative Contractors (MACs) may determine coverage of ~~other~~ *tests other than those described in Section B using* Next Generation Sequencing (NGS) ~~as a diagnostic laboratory test~~ when performed in a CLIA-certified laboratory, when ordered by a treating physician, when results are provided to the treating physician for management of the patient and when all the following conditions are met:

~~The patient has:~~

- the beneficiary has a cancer diagnosis ~~other than breast or ovarian cancer~~, clinical indications for germline (inherited) testing, *and* risk factors for germline (inherited) cancer ~~other than inherited breast or ovarian cancer~~;
- the test is ordered by a treating physician; *and*
- the beneficiary is seeking treatment and weighing medical management options based on germline mutation status, as recommended by NCCN guidelines and/or relevant evidence-based medical society guidelines.
- ~~not been previously tested using NGS.~~