American
Clinical Laboratory
Association

May 29, 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

Dear Ms. Syrek Jensen,

The American Clinical Laboratory Association (ACLA) appreciates the opportunity to comment on CMS's internally-initiated reconsideration of the National Coverage Determination 90.2, Next Generation Sequencing for Medicare Beneficiaries with Advanced Cancer (NCD).[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 next generation sequencing (NGS) technology is available when a Medicare beneficiary's physician has determined that it is necessary for medical management of the beneficiary.

Subject to the following comments, ACLA supports national coverage under the NCD for laboratory tests using NGS technology for Medicare beneficiaries with advanced stage cancers. We agree with CMS leadership that cancer patients should have enhanced access to expanded coverage of tests using NGS technology that can help guide medical management and support shared decision-making by doctors and patients about treatment options. Our comments aim to realize this promise of providing Medicare beneficiaries with access to analytically and clinically validated tests using state-of-the-art technology that has become the standard of care for many disease states.

However, national evidence-based consensus guidelines also support the use of germline-only tests using NGS technology in patients with early-stage cancers in certain circumstances, and ACLA believes that the Medicare Administrative Contractors should have the discretion to cover such tests when particular criteria are met. We also support the MolDx program's approach to coverage of laboratory tests using NGS technology in patients with diagnosed or suspected myeloid malignancies. ACLA takes this opportunity to share our views on the scope of the NCD, and we have provided suggested language for the text of the NCD.

We appreciate the Coverage and Analysis Group's engagement with ACLA and other stakeholders on this issue and we look forward to continued collaboration with you.

[1] National Coverage Analysis (NCA) Tracking Sheet for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R), *available at* https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=296&bc=ACAAAAAAQAAA&.

A. NGS as a Technology Platform

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 is not a class of tests – it is a test methodology within the available class of technologies in molecular testing, which includes PCR, qPCR, RT-PCR, Sanger sequencing, fluorescence in-situ hybridization (FISH), and microarrays, 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 other sequencing methods, but it can be more cost-efficient, allows for simultaneous interrogation of the entire genome, and can be used with samples with low-input DNA. Numerous validation studies of clinical assays using NGS technology have been published in peer-reviewed journals, underscoring the rapid maturation and uptake of the technology platform.[2] Further, a study involving more than 1,100 samples comparing an NGS-based hereditary breast and ovarian cancer test with traditional genetic testing showed 100 percent analytical concordance between the 29-gene BRCA1/BRCA2 NGS panel and the results of traditional genetic testing.[3] 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 laboratory-developed tests (LDTs) and with commercially-available kits that are cleared or approved by the FDA. A study published in JAMA Oncology in December 2017 compared the 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. The authors also noted that more than 60 percent of study participants using FDA-approved assays modified the approved assays to broaden clinical practice, rendering the tests LDTs.[4]

B. Germline-only testing using NGS technology in patients with stage I or II cancer

In the Decision Memo, CMS said it reviewed evidence directed at answering the question: "Is the evidence sufficient to conclude that [NGS] when used as a diagnostic test for

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[2] *See, e.g.*, Kurian AW *et al*. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J. Clin. Oncol. 2014, 32:2001-2009; Maxwell KN *et al*. Prevalence of mutations in a panel of breast cancer susceptibility genes in BRCA 1/2-negative patients with early-onset breast cancer. Genet Med 2014. doi: 10.1038/gim.2014.176; Chong HK *et al*. The validation and clinical implementation of BRCAplus: a comprehensive high-risk breast cancer diagnostic assay. PLoS One 2014, 9:e97408.

[3] Lincoln SE *et al*. A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. J. Mol. Diagn. 2015, 17:533-544.

[4] 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.

patients with advanced cancer meaningfully improves health outcomes?" The scope of the NCD reaches germline mutation testing using NGS technology, whether in combination with somatic mutation testing or alone, in patients with stage III or IV cancer who have not been tested with the same test using NGS technology for the same primary cancer diagnosis and who are seeking further treatment. We believe that Medicare Administrative Contractors (MACs) should have the discretion to cover germline-only testing using NGS technology in patients with stage I or II cancer when certain criteria are met.

We note that ACLA is not advocating for the use of germline-only testing with NGS technology as a screening tool for Medicare beneficiaries. We acknowledge that in the absence of signs and symptoms of cancer or a personal history of cancer in a Medicare beneficiary, germline-only testing used for purposes of screening is not a covered Medicare benefit. Our comments are limited to use of germline-only testing in patients with early-stage cancer.

1. Current Guidelines on Germline-Only Testing in Patients with Early-Stage Cancer

Germline testing in early-stage cancers currently is the standard of care for many types of cancers, and an NCD that removes existing Medicare coverage of the testing is not in the best interest of Medicare beneficiaries. Evidence-based professional guidelines support this and recognize the clinical utility of germline testing in many instances.

The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 28 leading cancer centers devoted to patient care, research, and education, develops guidelines for oncology care that favor evidence-based, consensus-driven management to ensure that all patients receive preventive, diagnostic, treatment, and support services that are most likely to lead to optimal outcomes. NCCN Guidelines are the recognized standard for clinical policy in cancer care and are the most thorough and frequently updated clinical practice guidelines available in any area of medicine. Two NCCN guidelines, Genetic/Familial High Risk Assessment: Breast and Ovarian and Genetic/Familial High Risk Assessment: Colorectal, are focused entirely on hereditary cancer assessment and include detailed clinical criteria for germline testing (which apply both to early-stage cancers and advanced cancers) and subsequent medical management recommendations.[5] In addition, numerous NCCN guidelines for treatment of cancer by site (*e.g.*, breast, ovarian, prostate, pancreatic, colorectal, and thyroid) mention germline mutation status as a consideration for certain treatment choices, including for early-stage cancer patients. For example, identification of a BRCA mutation in a woman with early-stage breast cancer leads to consideration of more extensive surgical treatment and follow-up breast surveillance using MRI, in addition to mammography. Another example is patients with medullary thyroid cancer, for whom germline RET proto-oncogene testing is recommended and for whom a positive result impacts pre-operative evaluation and the extent of resection.[6]

[5] NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High Risk Assessment: Breast and Ovarian, Version 3.2019 (Jan. 18, 2019); NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High Risk Assessment: Colorectal, Version 1.2018 (July 12, 2018).
[6] NCCN Clinical Practice Guidelines in Oncology, Thyroid Carcinoma; Version 1.2019 (March 28, 2019).

Specialty medical societies publish their own evidence-based consensus guidelines on optimal risk-stratification and treatment of cancers. In many cases, these guidelines include recommendations for germline testing in early-stage cancer patients under certain circumstances. For example, the American Society of Breast Surgeons' Consensus Guideline on Genetic Testing for Breast Cancer recommends that genetic testing be made available to all patients with a personal history of breast cancer and recognizes the value of multi-gene panel testing for detecting pathogenic variants related to hereditary cancer risk.[7] The American College of Gastroenterology guideline, "Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes," recommends that certain patients with a personal history of cancer should undergo germline mutation genetic testing for the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* genes.[8] Similar recommendations appear in a consensus statement by the U.S. Multi-society Task Force on Colorectal Cancer.[9] These and other medical society guidelines underscore the medical management value of germline testing in early-stage cancer patients, as well as those with advanced cancer.

In its 2016 revision to classification of myeloid neoplasms and acute leukemia, the World Health Organization added a section on myeloid neoplasms with germline predisposition, which includes cases of myelodysplastic syndrome, myelodysplastic syndrome/myeloproliferative neoplasm, and acute leukemia that occur on the background of a predisposing germline mutation. The updated WHO classification includes germline molecular findings with diagnostic importance that are associated closely with myeloid neoplasms.

2. Discretion for MACs to Cover NGS-Based Germline-Only Testing in Patients with Early-Stage Cancer

Our recommendation is that, in addition to the discretion afforded MACs to cover certain testing using NGS technology in beneficiaries with advanced stage cancers, the MACs should have the discretion to cover germline-only testing using NGS technology in patients with stage I or II cancer when certain criteria are met. Allowing the MACs to develop Local Coverage Determinations for germline-only testing in early-stage cancer patients would be a flexible approach that would accommodate technological advances and changes in evidence-based guidelines and 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-only mutation tests and other tests using NGS technology that a physician uses in medical management of a Medicare beneficiary. MACs have well-established methods for consulting with laboratories and other stakeholders, reviewing evidence, 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,

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[7] American Society of Breast Surgeons, Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer (2019) at 6, *available at* https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf.

[8] Syngal, RE *et al*. ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. Am. J. Gastroenterol. 2015 Feb; 110(2): 223-263.

[9] Giardiello, FM *et al.* Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-society Task Force on colorectal cancer. Am. J. Gastroenterol. 2014 Aug; 109(8):1159-79.

retaining the overly-broad non-coverage language in the NCD would lead to concerning and confusing 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-only testing and have covered it for some indications for several years. For example, as of 2017, every MAC had an LCD covering *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 current NCD language, which has the overall effect of removing existing coverage for early-stage cancer patients.

Below, we set forth the criteria under which we recommend a MAC should be permitted to cover germline-only testing in patients with stage I or II cancer:

- The test is performed in a CLIA-certified laboratory;
- The test is ordered by a treating physician;
- The patient has stage I or II cancer; and
- The patient 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 the guidelines referenced above or 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. We acknowledge that "not all medical society guidelines are created equal" and agree that it is important that MACs take into account consensus-based guidelines developed with rigorous peer-review.

C. Myeloid Malignancies and Suspected Myeloid 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." Myeloid malignancies are not staged according to a TNM staging system, nor are all myeloid 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 acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms as refractory

and/or metastatic cancers for purposes of Medicare coverage.[10] As such, under the terms of NCD 90.2, a test using NGS technology may be covered by the MAC when used in a patient with a diagnosis of one of these diseases when performed in a CLIA-certified laboratory and ordered by the treating physician.

Genetic testing underlies the classification of myeloid malignancies and has aided in the correct classification and prognostic tiering of these cancers. Expert society consensus recommendations and clinical practice guidelines (NCCN and the World Health Organization, among others), recommend laboratory evaluation of suspected or established hematologic cancers be subjected to genetic testing across numerous genes to identify clinically actionable, disease-relevant genetic alterations.[11] Tests using NGS technology in patients with myeloid malignancies reflect the standard of care and, as such, should not be denied to Medicare beneficiaries. Multiplex NGS testing has been recognized as an optimal and comprehensive laboratory testing methodology for routine clinical evaluation of hematologic and lymphoid diseases and has emerged as the current standard to guide clinical management decisions (including indications for target-specific therapy), improve prognostic risk stratification, and provide precise diagnostic sub-classification for patients with known or suspected myeloid diseases.

The approach taken by Palmetto GBA under the MolDx program is bolstered by evidence that more than 70 genes are clinically informative for the diagnosis, prognosis/risk stratification, and identification of targeted therapies for acute and chronic myeloid disorders.[12] Moreover, tests using NGS technology have been validated as reliable and reproducible methods for acute myeloid leukemia diagnosis. Well-designed NGS panels have been shown to be sufficient to guide clinical decision-making, with 100 percent concordance between NGS methods and traditional methods, and with NGS identifying more clinically relevant mutations.[13]

Coverage of a test using NGS technology in a patient with myeloid malignancy or suspected myeloid malignancy would be reasonable in that it would be conditioned on the test having completed a technical assessment by the MolDx program for the test's stated indications and the test would need to include at least the minimum genes for its intended use. Under the Draft LCD, patients without a diagnosis of a myeloid malignancy would need to have had an undefined cytopenia for greater than six months or have had other possible causes of symptoms reasonably ruled out. In combination with the criteria for MAC coverage in the NCD, these conditions ensure that a test using NGS technology in a patient with a diagnosed or suspected myeloid malignancy is reasonable and medically necessary and therefore coverable by Medicare.

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[10] Proposed Local Coverage Determination (LCD): 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&.

[11] *See, e.g.*, NCCN Clinical Practice Guidelines in Oncology, Myeloproliferative Neoplasms; Arber D.A. *et. al*. 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016, 127(20): 2391-2405.

[12] Mukherjee, S, *et al*. Addition of chromosomal microarray and next generation sequencing to FISH and classical cytogenetics enhances genomic profiling of myeloid malignancies. Cancer Genet. 2017. 216-217:p. 128-141.

[13] Alonso, CM *et al.* Clinical utility of a next-generation sequencing panel for acute myeloid leukemia diagnostics. J. Mol. Diagn. 2019 Mar; 21(2): 228-240.

D. Use of NGS-Based Tests for Minimal Residual Disease is Unresolved

The final NCD Decision Memo did not address the issue of coverage for use of 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.[14] 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.[15] This approach also is discussed in the recommendations of the International Myeloma Working Group.[16] Recent NCCN guidelines for acute lymphoblastic leukemia (ALL) also reference NGS methods for disease assessment in adults at baseline and following different treatment phases.[17]

Repeat testing using NGS technology in patients with multiple myeloma and ALL should not be foreclosed or complicated by language in the 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 hematological cancer guidelines also support MRD assessment at relevant points in a patient's cancer care, and it is likely that NGS increasingly will be a recommended method for such assessments.[18] CMS should ensure that Medicare beneficiaries with hematological 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. Revised Language for NCD 90.2

To effectuate the foregoing recommendations, ACLA suggests that the language of sections C and D of NCD 90.2 be revised as set forth below. Deletions are struck-through and additions are in italics.

> ~~**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.~~

[14] 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.
[15] NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma, Version 2.2019 (Nov. 16, 2019) at MYEL-D 1, 3.
[16] International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-46.
[17] NCCN Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version 2.2019 (May 15, 2019) at ALL-F.
[18] *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.

~~D~~*C*. Other

Effective for services performed on or after March 16, 2018, Medicare Administrative Contractors (MACs) may determine coverage of other NGS ~~as a~~ diagnostic laboratory tests for patients with cancer ~~only~~ when the test is performed in a CLIA-certified laboratory, ordered by a treating physician, and the patient ~~has~~ *meets the criteria in section C.1. or C.2.:*

1. The patient has:

- Either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, and
- Either has not been previously tested using the same NGS test for the same primary diagnosis of cancer *(other than for minimal residual disease assessment),* or repeat testing using the same NGS test was performed only when a new primary cancer diagnosis is made by the treating physician, and
- Decided to seek further cancer treatment.

2. The patient has:

- *Stage I or stage II cancer, and*
- *Decided to seek medical management options, recommended by NCCN guidelines and/or relevant evidence-based medical society guidelines, based on germline mutation status.*

In order to allow a reasonable amount of flexibility in coverage of tests using NGS technology that can accommodate advances in the technology and in the evidence of clinical utility of such tests in diagnosing and managing different disease states, the broad non-coverage language should be removed from the NCD altogether.

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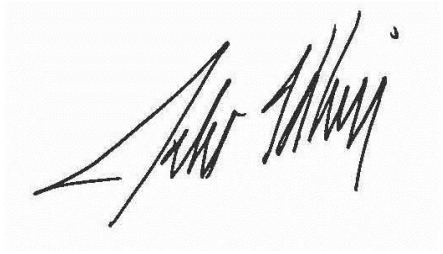
Thank you for your consideration of ACLA's comments and for your continued engagement with ACLA on this and other issues.

Sincerely,



Julie Khani, President
American Clinical Laboratory Association