



ASSOCIATION FOR MOLECULAR PATHOLOGY
Education. Innovation & Improved Patient Care. Advocacy.
6120 Executive Boulevard, Suite 700, Rockville, Maryland, 20852
Tel: 301-634-7987 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

November 27, 2019

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

Re: Reconsideration of the National Coverage Determination on Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Dear Ms. Jensen,

The Association for Molecular Pathology (AMP) is pleased to offer comments on the Centers for Medicare and Medicaid Services' (CMS) Proposed Decision Memo on Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer, pursuant to CAG-00450R. AMP is an international medical and professional association representing approximately 2,500 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 academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

AMP appreciates CMS' engagement with the oncology community during the reconsideration process that resulted in the release of this Proposed Decision Memo. While we remain concerned about the implications of including germline testing within the scope of this National Coverage Determination (NCD), both based on the intent of the policy and evidence reviewed during its initial development¹, we thank CMS for reviewing the evidence and recognizing that it is sufficient to expand coverage. However, upon our review we have concerns that the proposed policy falls short in aligning fully with the current diagnostic landscape for germline NGS-based testing as well as the needs of Medicare beneficiaries with cancer. Below we outline our concerns as well as recommend changes to the proposed NCD language that we feel will help to provide an appropriate coverage pathway for Medicare beneficiaries. The recommended edits to the proposed policy contained within [Appendix A](#) will result in the expanded access to germline testing for patients with cancer for which CMS acknowledges sufficient evidence exists, and we urge CMS to incorporate these edits into the final policy.

The Proposed Decision Memo will restrict, not expand coverage for breast and ovarian germline tests.

As drafted, CMS would provide national coverage only for NGS-based breast and ovarian germline tests that are either FDA approved or cleared. However, there are currently no tests that meet this coverage criteria. CMS provides Medicare Administrative Contractors (MACs) discretion to cover germline NGS-based tests for cancers but excludes NGS-based tests for breast and ovarian cancer that do not meet the

¹ <https://www.amp.org/AMP/assets/AMP-Comments-NCDforNGSReconsideration-CAG-00450R-FINAL.pdf?pass=42>

national coverage criteria from that coverage pathway. The MACs may interpret this to mean that they cannot otherwise cover NGS-based germline testing for breast and ovarian cancer patients. Thus, while CMS acknowledges the evidence is sufficient to expand coverage, the language as drafted has the opposite intended effect.

Within the existing NCD and the new manual language additions in the Proposed Decision Memo, CMS has bifurcated the policy to allow national coverage for FDA approved and cleared tests (given the test and the patient meet certain criteria) and MAC discretion for all other tests. AMP disagrees that FDA approved or cleared tests are the only tests that warrant national coverage for a number of reasons, including most notably that the evidence reviewed to make that determination is based on tests that are not FDA cleared or approved. While AMP would prefer that CMS expand coverage to include both non-FDA reviewed tests and those approved and cleared by the FDA, AMP sees great value in providing discretion to MACs as their ability to develop local coverage determinations (LCDs) for these tests has allowed coverage to continue and ensure there are no gaps in care. However, the proposed germline language as drafted does not achieve that and the inclusion of the language “other than breast and ovarian cancer” in the local coverage pathway prevents MACs from developing LCDs for these cancers. This mandate coupled with the fact that no FDA approved or cleared NGS-based germline tests exist for breast and ovarian cancer create a *de facto* non-coverage policy for germline breast or ovarian NGS-based testing. Non-coverage for germline breast or ovarian cancer would remain until the eventual development of FDA approved or cleared tests. Additionally, even if FDA were to clear or approve one test that meets CMS’s proposed coverage criteria, the policy would continue to restrict patient access by unnecessarily create a testing monopoly.

Therefore, it is important that the final NCD allow MACs to retain discretion to cover germline NGS-based tests for breast and ovarian cancer patients in order to maintain the local coverage pathway and prevent gaps in care. This will require CMS to expand the conditions under which the MACs can provide local coverage for germline testing. AMP recommends revisions to the manual in [Appendix A](#) below that would maintain national coverage for FDA approved and cleared NGS-based germline testing, while still allowing MACs to develop LCDs providing coverage for NGS-based testing for breast and ovarian cancers.

Language clarification is needed to ensure proper implementation of the proposed policy

It is critical that any additions to this NCD are drafted clearly to avoid any confusion with regards to scope and parameters for NGS-based testing for cancer. From our review, is not clear how the new language that is outlined using red font relates (or does not relate) to the existing NCD language. It is our understanding that the new language specifically relates to germline testing but that is not explicitly stated in the Proposed Decision Memo, and the new language is only delineated by date. Below, we address additional specific issues with the draft language and request edits to the Proposed Decision Memo to mitigate confusion and potentially damaging consequences.

Staging

CMS notes within Section A of the Proposed Decision Memo that “the scope of this review is limited to next generation sequencing of germline mutations to identify patients with inherited cancer at any stage.” From our review, the language in the Proposed Decision Memo includes coverage of germline testing that is inclusive of all stages, yet this is not explicitly stated in the germline section added to the proposed manual language in Appendix B, Section B. Since CMS did include language specifying the

stages covered for somatic testing in the policy, we request that CMS add clarifying language to the germline language in the manual that indicates it applies to inherited cancers at any stage as indicated in Section A of the Proposed Decision Memo. Additionally, since the germline language is for cancer at any stage, the title of the NCD should be revised as it implies the policy is only for Medicare patients with advanced cancer. Within [Appendix A](#) below we have provided suggested language that is consistent with the language used to define the scope of current reconsideration.

Patient criteria redundancy

In the same section describing patient characteristics for germline testing, we found the third bullet point in Sections B and D of the proposed manual language, which addresses risk factors for germline cancer, to be redundant with the first two criteria listed. If a patient meets the other criteria in that they have cancer and clinical indications for germline testing, they, by default, possess risk factors for that inherited cancer. AMP urges that the third bullet point be struck from the proposed manual language in order to avoid confusion and eliminate redundancy when the policy is implemented.

Repeat Testing for Germline Testing

The requirement within the Proposed Decision Memo that a patient “has not been previously tested using NGS” is vague and could be interpreted very broadly, resulting in restricted patient access to medically necessary testing using NGS. At a high level, this addition as drafted potentially creates confusion as NGS-based testing is used for other clinical indications separate from cancer. For example, an NGS-based molecular microbiology test may be ordered to help diagnose an infection. As drafted, the general nature of the language could be read to mean that any Medicare beneficiary who received any NGS-based test previously for any indication could not receive germline testing to provide information on the management of their cancer.

Additionally, the stipulation with the new proposed germline language that the patient has “not been previously tested using NGS” and the lack of clarity it creates has implications for both somatic and germline NGS-based tests, most significantly for Medicare beneficiaries with cancer that may require more than one NGS-based test in order to properly diagnose and manage treatment for the patient. There are many situations in which a person is diagnosed with cancer and the oncologist orders somatic NGS-based testing. If a mutation is found that is also implicated in inherited cancers, such as a mutation in a *BRCA* gene, the standard practice is to refer the patient for germline testing to determine if the mutation is inherited in order to properly treat and manage the patient’s cancer. From our review of the requirement that a patient “has not been previously tested using NGS,” coverage of a germline NGS-based test in this case would not be allowed. Consequently only tests utilizing older, less-advanced, and more expensive non-NGS methods will be eligible for Medicare coverage.

Moreover, there exists a discrepancy between the language used regarding repeat testing in the indications for germline versus that for somatic testing. The provision for germline testing states that a patient has “not been previously tested using NGS”, while for somatic testing it states that a patient “has 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.” Thus, we request that this language be revised. Our recommendation to this section, provided within [Appendix A](#) below, work to more closely mimic the language used in the somatic section of the NCD and establish limitations around repeat testing for germline that align with clinical practice needs.

Non-Coverage Provision

AMP continues to have concerns about the language in Section C of the Medicare National Coverage Determinations Manual language which outlines parameters for tests that are nationally non-covered. Similar language was removed from the original NCD when it was finalized in March 2018 after stakeholders, including AMP, commented that the proposed coverage criteria was too broad and may be construed to include diagnostic laboratory tests using NGS for conditions other than oncology.² We remain concerned about this section for the same reasons. It is unclear why the agency chose to restore Section C in this Proposed Decision Memo, and we request that CMS remove the non-coverage provisions in Section C from the final NCD.

NGS is only one specific type of sequencing methodology. CMS should review evidence and practice guidelines for clinical indications for testing, not the sequencing method.

In our comments dated May 29, 2019, we expressed our concern that providing coverage for testing based upon the technology (NGS-based), rather than for testing for the biomarker, is a fundamentally flawed construct that will require CMS to revisit this policy on a regular basis. We wish to reiterate these concerns, as we believe this construct will necessitate the need for regular reconsideration of this policy in order for it to align with clinical practice. Evidence-based guidelines from the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the American Society of Hematology, AMP, the College of American Pathologists, and the World Health Organization support the clinical utility of testing for molecular alterations in various diseases but they do not specify the specific technologies that should be utilized to detect those alterations. These groups recognize that such alterations can also be detected by non-NGS based technologies. Therefore, it would be more appropriate for a coverage policy to address the genetic alterations, cancer types, and/or targeted therapy combinations that together define clinical relevance rather than a specific methodology. AMP continues to urge CMS to adopt this approach moving forward and consider evidence that examines the underlying use of assessing certain biomarkers or genes in its assessment. As an example, a recent paper demonstrated that the results of NGS testing proficiency testing for *BRAF*, *EGFR*, and *KRAS* somatic mutations are equivalent or superior to that performed using other methods.³

Again, AMP thanks CMS for reconsidering this NCD based on stakeholder concerns and providing the opportunity to provide these comments. We are confident the language modifications within [Appendix A](#) will work to ensure that Medicare beneficiaries have access to medically appropriate testing. AMP is committed to working with the CMS Coverage and Analysis Group (CAG) to further modify this coverage policy to assure that patients continue to have access to clinically appropriate NGS-based testing. We

² <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&NCDId=372&ncdver=1&CoverageSelection=National&Keyword=next+generation+sequencing&KeywordLookUp=Title&KeywordSearchType=And&IsPopup=y&bc=AAAAAAAAQAAA&>

³Surrey, L et al. Next-Generation Sequencing (NGS) Methods Show Superior or Equivalent Performance to Non-NGS Methods on BRAF, EGFR, and KRAS Proficiency Testing Samples Arch Pathol Lab Med 2019 Aug;143(8):980-984 <https://www.ncbi.nlm.nih.gov/pubmed/30865489>

look forward to working with you during this process to provide evidence and expert opinion on NGS-based testing. If you have any questions, please contact Tara Burke at tburke@amp.org.

Sincerely,

Karen E. Weck, MD, FCAP
President, Association for Molecular Pathology

Appendix A

Below, AMP provides recommended revisions to the proposed manual language. We have provided the full text of the manual language included in Appendix B of the Proposed Decision Memo for clarity. Please note that all changes are highlighted in yellow with additions to the proposed language bolded in black and any recommended deletions are noted by striking through the text.

Medicare National Coverage Determinations Manual Draft

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90.2 Next Generation Sequencing (NGS) for Patients with **Advanced** Cancer
(Rev. 215, Issued: 04-10-19, Effective: 03-16-18, Implementation: 04-08-19)

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, such as when used as a companion in vitro diagnostic test.

Patients with cancer can have 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 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 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; 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.

Effective for services performed on or after [Month/XX] [Day/XX], [20XX], the CMS, proposes that 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 **at any stage**;
- clinical indications for germline (inherited) testing,
- **risk factors for germline (inherited) cancer breast or ovarian cancer; and**
- not been previously tested using **the same germline NGS test**.

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 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 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 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; 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 was performed only when a new primary cancer diagnosis is made by the treating physician; and,
- decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

Effective for services performed on or after [Month/XX] [Day/XX], [20XX], Medicare Administrative Contractors (MACs) may determine coverage of other 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:

- a cancer diagnosis **at any stage other than breast or ovarian cancer,**
- clinical indications for germline (inherited) testing,
- **risk factors for germline (inherited) cancer other than inherited breast or ovarian cancer, and**
- not been previously tested **using the same germline NGS test.**