



National Comprehensive  
Cancer Network®

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

RE: National Coverage Analysis (NCA) Tracking Sheet for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R)

Dear Ms. Syrek Jensen:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R) as it relates to evidence supporting the use of NGS for identification of germline mutations.

As an alliance of 28 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN is a developer of authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. NCCN's mission is to improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 percent of cancers affecting patients in the United States. NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives.

The NCCN Drugs & Biologics Compendium (NCCN Compendium®) has been recognized by the Centers for Medicare and Medicaid Services (CMS) and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for establishment of coverage policy and coverage decisions regarding off-label use of anticancer and cancer-related medications. Further, NCCN Guidelines and Library of Compendia products are utilized by commercial payers that represent more than 85 percent of covered lives in the United States.

The NCCN Biomarkers Compendium® is a tool developed to identify the appropriate use of biomarkers to screen, diagnose, monitor, and provide predictive and prognostic

**NCCN Member Institutions**

- Abramson Cancer Center at the University of Pennsylvania
- Fred & Pamela Buffett Cancer Center
- Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute
- City of Hope National Medical Center
- Dana-Farber/Brigham and Women's Cancer Center Massachusetts General Hospital Cancer Center
- Duke Cancer Institute
- Fox Chase Cancer Center
- Huntsman Cancer Institute at the University of Utah
- Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
- The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
- Robert H. Lurie Comprehensive Cancer Center of Northwestern University
- Mayo Clinic Cancer Center
- Memorial Sloan Kettering Cancer Center
- Moffitt Cancer Center
- The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
- O'Neal Comprehensive Cancer Center at UAB
- Roswell Park Comprehensive Cancer Center
- Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
- St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center
- Stanford Cancer Institute
- UC San Diego Moores Cancer Center
- UCSF Helen Diller Family Comprehensive Cancer Center
- University of Colorado Cancer Center
- University of Michigan Rogel Cancer Center
- The University of Texas MD Anderson Cancer Center
- University of Wisconsin Carbone Cancer Center
- Vanderbilt-Ingram Cancer Center
- Yale Cancer Center/ Smilow Cancer Hospital

information for the treatment of patients. Based directly on the NCCN Guidelines, the NCCN Biomarkers Compendium contains information designed to support decision-making around the use of biomarker testing in patients with cancer. The goal of the NCCN Biomarkers Compendium is to provide essential details for those tests which have been approved by NCCN Guidelines Panels and are recommended by the NCCN Guidelines. Tests that measure changes in genes or gene products and which are used for diagnosis, screening, monitoring, surveillance, or for providing predictive or prognostic information are included in the NCCN Biomarkers Compendium. General information on appropriate methodologies for biomarker testing is provided, focusing on the biology or abnormality being measured rather than on commercially available tests or test kits. The NCCN Biomarkers Compendium aims to ensure that patients have coverage and access to appropriate biomarker testing based on the evaluations and recommendations of NCCN Guidelines Panel members.

### **NCCN Evidence Base and Guidelines Development Process**

The proposed decision memo inaccurately states that the NCCN Guidelines® are not evidence-based. As such, NCCN would like to provide clarifying information on our guidelines development process and the evidence-base for our guideline recommendations. The NCCN Guidelines are composed of recommendations based on the best evidence available at the time they are derived. NCCN library of guidelines contain 28,000 references to evidence. Additionally, the guidelines submitted for consideration, Genetic/Familial High-Risk Assessment Breast and Ovarian and Genetic/Familial High-Risk Assessment: Colorectal, contain respectively 508 and 255 references to evidence.

The development of the NCCN Guidelines is an ongoing and iterative process based on a critical review of the best available evidence and derivation of recommendations by a multidisciplinary panel of experts in the field of cancer. Because new data are published continuously, it is essential that the NCCN Guidelines also be continuously updated and revised to reflect new data and new clinical information. The NCCN Guidelines are reviewed and updated on a continual basis to ensure that the recommendations take into account the most current evidence. All active NCCN Guidelines are reviewed and updated at least annually. In 2018, NCCN published 185 guideline updates to ensure guidelines reflect the most up-to-date and comprehensive evidence available.

The annual review process is driven largely by the annual Institutional Review performed for each of the NCCN Guidelines. However, interim Panel meetings are conducted throughout the year, as needed, based upon new evidence from studies evaluating existing agents or regulatory approvals of new drugs or biologics that may change clinical practice standards.

Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. Panels are charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. Recommendations or changes to existing recommendations are agreed upon by Panel Members following review and discussion of the evidence during the Panel meetings. The Panel Members deliberate on the interpretation of the clinical evidence, and vote on how the evidence should be incorporated into the existing Guidelines.

### **NCCN Guideline References within Proposed Decision Memo**

NCCN would like to emphasize the clear distinction between tumor testing for patient therapeutic guidance in our cancer specific guidelines, as opposed to germline testing noted in our Genetic/Familial High-Risk recommendations to inform risk-reduction and screening in affected individuals and their family members. Within the proposed decision memo, CMS cites submitted NCCN guidelines but lists information derived from NCCN's Breast Cancer Guidelines and Ovarian Cancer Guidelines rather than the Genetic/Familial High-Risk Assessment Breast and Ovarian Guidelines. The NCCN Breast Cancer Guidelines and Ovarian Cancer Guidelines include treatment recommendations based on germline mutation status. However, the information contained within the current NCCN Breast Cancer Guidelines that CMS cites is not relevant to the clinical utility of NGS for germline testing, as these Guidelines provide no mention of NGS for germline mutation testing. Additionally, the information included from the NCCN Ovarian Cancer Guidelines pertains to NGS for tumor testing only. Like the breast cancer treatment guidelines, the ovarian cancer treatment guidelines provide no mention of NGS for germline mutation testing. NCCN respectfully requests that CMS refer to and consider recommendations in the Genetic/Familial High-Risk Assessment Breast and Ovarian and Genetic/Familial High-Risk Assessment: Colorectal Guidelines. In addition, NCCN respectfully requests that CMS remove the content from the treatment guidelines that are currently cited within the proposed decision memo.

Both the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective than single-gene testing. Besides breast and ovarian cancers, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian also recommend consideration of multi-gene germline testing in the context of pancreatic cancer, which is thought to have a familial or hereditary component in approximately 10% of cases.<sup>1,2</sup>

Finally, CMS does not include the submitted Genetic/Familial High-Risk Assessment: Colorectal Guidelines within this section, although it was submitted. NCCN notes that there is evidence to support germline multi-gene testing in patients with colorectal cancer in certain clinical circumstances. Examples of clinical scenarios for which multi-gene testing should be considered include:<sup>3</sup>

- Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome (ie, family meets both BRCA-related breast and/or ovarian cancer and Lynch Syndrome clinical criteria or family history of young-onset colorectal cancer and oligopolyposis)
- Colonic polyposis with uncertain histology
- Family cancer history does not meet established testing guidelines, but consideration of inherited cancer risk persists and an appropriate panel is available
- Individuals concerned about cancer predisposition for whom family cancer history is limited or unknown
- Second-line testing for inherited cancer risk when first-line testing has been inconclusive
- Adenomatous polyposis

Clinically appropriate recommendations from the NCCN Guidelines for Genetic/Familial High-Risk Assessment should be used as a reference tool when understanding patient populations that would benefit from NGS tests of germline mutations. Both the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide clinical criteria, independent of the disease stage or presence of disease, for individuals with an increased genetic risk who could benefit from NGS-based quantification for hereditary cancers (Appendix 1 and Appendix 2). Once clinical criteria for multi-gene testing of germline mutations is met, the NCCN Guidelines outline specific management algorithms that might include intensive cancer surveillance, screening, or consideration of preventative medical therapies. In the proposed decision memo, CMS states that studies on colorectal cancer and Lynch syndrome were not included in the evidence review because the studies did not assess mortality. NCCN notes that timely identification of individuals at risk for hereditary cancers offers an opportunity to intervene to prevent the development of cancer which may ultimately impact mortality.

## **Proposed Decision Memo Language**

CMS proposes to cover NGS testing for patients with ovarian or breast cancer, clinical indications for germline testing, risk factors for germline breast or ovarian cancer, who have not been previously tested using NGS. Additionally, CMS proposes to allow Medicare Administrative Contractors (MACs) to cover NGS testing when for patients with a cancer diagnosis other than breast or ovarian cancer, clinical indications for germline testing, risk factors for germline cancer other than inherited breast or ovarian cancer, and who have not been previously tested using NGS. NCCN agrees with CMS that there is evidence to support NGS testing in patients with breast and ovarian cancer. Additionally, NCCN notes there is data available to support NGS for germline testing for hereditary syndromes associated with pancreas and colon cancers.<sup>1,2,3</sup>

NCCN has heard concerns from patient advocacy groups that the proposed decision memo as currently worded may cause confusion among providers. Specifically, the proposed decision memo states that a patient must have breast or ovarian cancer, and clinical indications for germline testing, and risk factors for germline testing. FORCE specifically notes that, for instance, all women with ovarian cancer meet clinical guidelines for germline testing. NCCN agrees with FORCE in their comments that this language may be confusing or duplicative.

NCCN has also heard concern from both providers and patient advocacy groups that as written, the proposed decision memo indicates coverage only of NGS tests that are FDA approved or cleared for germline testing. To date, none of the NGS products on the market are approved specifically for germline testing and are unable to distinguish between germline and somatic mutations. As such, NCCN agrees with the concern of patient and provider groups that this requirement may cause patient access issues.

Additionally, patient advocates have expressed concern about limiting patients to one NGS test. NCCN recommends updating the language to cover additional NGS testing when the panel incorporates new or different potentially pathogenic variants.

NCCN suggests that simplifying the NCD language will address the issues noted above and make the language more appropriate for germline testing rather than somatic testing. NCCN proposes CMS revise the NCD language to read:

*A. The Centers for Medicare & Medicaid Services (CMS) proposes that the evidence is sufficient to expand coverage of Next Generation Sequencing (NGS) as a diagnostic laboratory test when performed in a CLIA-certified laboratory, when ordered by a treating physician for management of the patient and when all the following conditions are met:*

*The patient has:*

- *clinical indications for germline (inherited) testing,*
- *risk factors for germline (inherited) cancer, and*
- *not been previously tested using NGS, or if the proposed panel incorporates new or different potentially pathogenic variants*

NCCN again appreciates the opportunity to comment on CMS' Proposed Decision Memo for NGS for Medicare beneficiaries with advanced cancer as it relates to evidence supporting the use of NGS for identification of germline mutations. NCCN requests that CMS consider coverage consistent with nationally recognized, continuously updated, and evidence-based guidelines such as the NCCN Guidelines to ensure Medicare beneficiaries have access to the most up-to-date recommendations. Additionally, NCCN respectfully requests that CMS remove references to the Breast and Ovarian Cancer treatment guidelines and instead refer to the NCCN Genetic/Familial High-Risk Assessment Breast and Ovarian Guidelines and the NCCN Genetic/Familial High-Risk Assessment: Colorectal Guidelines. Additionally, NCCN encourages CMS to consider revised wording in the proposed decision memo that would not impede patient access to clinically appropriate germline multi-gene testing. We would welcome the opportunity to discuss our comments further and look forward to working together to ensure access to high quality, high value care for patients with cancer. Thank you for your time and consideration of our comments.

Sincerely,



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## References

1. Chaffee KG, Oberg AL, McWilliams RR, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. *Genet Med* 2018;20:119-127.
2. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA* 2018;319:2401-2409.
3. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal (Version 2.2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: [NCCN.org](http://NCCN.org). Accessed [November 2019]. To view the most recent and complete version of the NCCN Guidelines®, go online to [NCCN.org](http://NCCN.org).