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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) reconsideration of the National Coverage Determination (NCD) 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 supports the parallel review process that provides for concurrent review by the FDA for approval and by CMS for coverage that led to the development of this NCD for NGS. We applaud CMS for recognizing the value of precision oncology diagnostics in the care of cancer patients in this coverage policy. However, we remain concerned that the final NCD would have a negative effect on patient access to clinically appropriate germline testing as we have outlined in both our correspondence and conversations to date. AMP is committed to working with the CMS Coverage and Analysis Group (CAG) during this reconsideration process to develop a coverage policy that assures patients retain access to clinically appropriate NGS-based testing.

We thank CMS for issuing a reconsideration in response to stakeholder concern[1] that emerged after AMP and other stakeholders reviewed the NCD's implementation instructions. Stakeholders were not aware that NGS-based germline testing was within the scope of the final policy and were made aware when the agency's transmittal to the Medicare Administrative Contractors (MACs) was published with instructions that both germline and somatic tumor NGS-based testing were non-covered for Medicare beneficiaries with early-stage cancer. AMP believes that the NCD's inclusion of early stage NGS-based testing for germline mutations represents significant policy overreach that will have unintended consequences on the care delivered to Medicare beneficiaries, particularly those who may have a genetic predisposition to cancer based on a family history or other relevant criteria.

[1] https://www.amp.org/AMP/assets/File/advocacy/Group_Stakeholder_Letter_NGSNCD-FINAL-1-31-2019.pdf

AMP believes that CMS should not have included early stage NGS-based germline testing within the scope of the NCD, resulting in non-coverage for this testing. Its inclusion was inappropriate based on the intent of the policy and evidence reviewed during its development. On November 17, 2017, CMS received a formal request from Foundation Medicine, Inc. to initiate a national coverage analysis (NCA) for comprehensive genomic profile testing with F1CDx, a next generation sequencing comprehensive genomic profile (CGP) for solid tumors. In response, CMS developed this NCD to address the rising demand for NGS-based solid tumor testing and the evidence reviewed during the policy's development focused exclusively on this testing. The only evidence cited related to germline testing was that performed in conjunction with somatic tumor testing. It did not consider evidence related to germline only testing, including germline testing in non-advanced cancer patients. We could not identify the evidence reviewed to evaluate NGS-based germline-only testing in cancer, the agency's responses to public comments on this topic, the rationale for non-coverage of early stage NGS-based germline testing, or the public data (other than proprietary data) considered when evaluating coverage in the final decision memorandum as required by the Social Security Act § 1862(l)(3)(c). Excluding NGS-based germline testing for early stage cancer from the NCD's scope is the most appropriate course of action in these circumstances and is consistent with the original intent of the NCD.

Specifically Delegate Coverage Authority to the MACs if CMS Cannot Limit the Policy's Scope

Under the current NCD for NGS, it is our understanding that coverage for germline tests is as follows: germline tests approved or cleared by the FDA as a companion in vitro diagnostic for advanced cancer are nationally covered and MACs retain the discretion to develop LCDs for all other NGS-based germline tests for advanced cancer patients. **If CMS believes that the statute prohibits this approach (i.e., excluding as out of scope all other NGS-based germline testing as described above), AMP recommends that the coverage section of the NCD specifically delegate the authority to cover NGS-based germline testing for *non-advanced* cancers to the MACs and CMS maintains national coverage for germline tests that have FDA approval or clearance and are used as a companion in vitro diagnostic for advanced cancer.**

The agency should consider the following issues and evidence if it cannot exclude NGS-based germline testing from the scope of the policy.

NGS-based testing for detecting early stage germline mutations has broad clinical utility and should not be pigeonholed into a national coverage policy that CMS formulated based on evidence for somatic cancer testing. Doing so, as we have seen, has significant downstream consequences for patients. For example, the vast majority of laboratories performing testing for Hereditary Breast and Ovarian Cancer Syndrome (HBOC) today do so using NGS-based methods. Testing for HBOC is indicated in select symptomatic patients under age 75, including Medicare patients, with diagnosis of a related cancer and an appropriate family history. Current management for patients with this syndrome, including patients over age 65, includes increased patient monitoring and in many cases risk reducing surgical intervention. If testing for HBOC is appropriate in Medicare patients, there appears to be no rationale for the non-coverage of BRCA testing by NGS while covering it when performed by older, more costly methods (i.e., Sanger sequencing). Allowing the MACs to continue to develop local coverage determinations (LCDs) for early stage NGS-based germline testing will reinstate coverage for germline testing for patients that existed before the NCD's effective date.

AMP believes it is imperative that MACs continue to have the authority to promulgate local coverage policies for the rapidly evolving area of germline testing in early stage cancer patients to allow Medicare policies to more effectively adapt to the changing standards of care reflected in updates or creation of new evidence based guidelines. Additionally, the CAG should recognize that the indications under an FDA-approved or cleared diagnostic laboratory test can be very narrow and that there are many appropriate additional indications

requiring coverage both for FDA-approved companion diagnostic NGS-based tests and other non-FDA approved NGS-based tests. For example, an NGS-based test may be used in a patient with advanced metastatic breast cancer according to FDA labeling to determine eligibility for targeted therapy, or an NGS-based germline test may be used in an early stage breast cancer patient to identify the need for increased monitoring or the possibility of a double mastectomy.

CMS provided this comment opportunity to evaluate the evidence available for tests of germline mutations to identify those with hereditary cancer who may benefit from targeted treatments based on results of these germline tests. Clinical use of germline testing is not limited to advanced cancer patients or FDA-approved or cleared companion diagnostics. This is a growing and dynamic field of testing with broad applicability for patients. Currently, clinical utility for germline tests in cancer patients exists for selection of various treatments including selection for targeted therapy, chemotherapy treatment, avoidance of certain treatments (contraindications), determination of appropriate surgery options and disease monitoring. The results of germline testing for Medicare beneficiaries inform clinical decision-making and may result in the use of targeted treatments as described above. Thus, in this context, "targeted treatments" should be defined broadly to be inclusive of all these clinical uses. We urge CMS to adopt this as a definition of targeted treatments moving forward.

There are multiple clinical scenarios and clinical guideline recommendations that support the varied uses that tests to analyze germline mutations can have on treatment targeted to the patient. Clinical guidelines support germline testing for various clinical uses and based on the evidence included in these comments, AMP believes there is a sufficient evidentiary basis to provide the MACs with the authority to cover NGS-based germline testing.

Multiple National Comprehensive Cancer Network (NCCN) guidelines address germline testing to guide treatment and management in early stage cancer patients including breast and ovarian cancer, colorectal cancer, pancreatic adenocarcinoma, and thyroid carcinoma.[2,3,4,5] Moreover, the NCCN Guidelines for BRCA-related Breast and/or Ovarian Cancer Syndrome and the NCCN Guidelines for Genetic/Familial High-Risk Assessment related to Colorectal Cancer[6] set out criteria where multi-gene testing is recommended.[7] This includes for certain individuals with a BRCA-related cancer, regardless of family history, in order to determine eligibility for a targeted treatment. Several NCCN treatment guidelines for BRCA-related cancers recommend treatment with PARP inhibitors for patients with germline BRCA 1/2 mutations, since they have been found to be beneficial in this patient population.

Additionally, multiple medical specialty and subspecialty organizations publish clinical practice guidelines to provide guidance and recommendations for germline testing in cancer to dictate medical management such as determination of appropriate surgery options and patient monitoring. The Society of Gynecologic Oncology (SGO) recommends that women diagnosed with epithelial ovarian, tubal, and peritoneal cancers receive genetic counseling and be offered genetic testing, even in the absence of a family history.[8] This is because germline

[2] NCCN Guidelines Version 3.2019. Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer.
[3] NCCN Clinical Practice Guidelines in Oncology, Genetic/Familial High Risk Assessment: Colorectal.
[4] NCCN Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma; Version 2.2019 (Apr. 9, 2019).
[5] NCCN Clinical Practice Guidelines in Oncology, Thyroid Carcinoma; Version 1.2019 (March 28, 2019).
[6] NCCN Guidelines Version 1.2018 for Genetic/Familial High-Risk Assessment related to Colorectal Cancer.
[7] NCCN Guidelines Version 3.2019. Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer.
[8] SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer.

BRCA1 and BRCA2 mutations account for 15 percent of invasive ovarian carcinomas, and would allow for personalized prevention to high-risk individuals, including more intensive screening and risk-reducing surgery.

The 2019 American Society of Breast Surgeons (ASBrS) 2019 guidelines recommend that genetic testing should be offered to each patient with breast cancer, either newly diagnosed or with a family history, since identification of a mutation may impact local treatment recommendations and systemic therapy.[9] For example, identifying that a breast cancer patient has a BRCA1 pathogenic variant provides that patient the opportunity to learn of her elevated risk for contralateral breast cancer and for ovarian cancer and allows the opportunity to provide education on ways to reduce those risks. The ASBrS guidelines also recommend multi-gene panel testing for patients who qualify for hereditary breast cancer testing to more efficiently and cost-effectively evaluate genes that confer risk and impact patient management recommendations.

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin also states that "clinical genetic testing for gene mutations allows more precise identification of those women who are at an increased risk of inherited breast cancer and ovarian cancer. For these individuals, screening and prevention strategies can be instituted to reduce their risk."[10]

Germline testing is valuable not only in the determination of treatment options but may also provide valuable information to indicate that a patient should avoid certain treatments (i.e., contraindications). For example, in Li-Fraumeni Syndrome patients should avoid both diagnostic and therapeutic radiation as such treatments in these patients can lead to induction of secondary malignancies. [11] Additionally, Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is a condition that affects many areas of the body and increases the risk of developing various cancerous and noncancerous tumors. Radiation therapy in these patients should be avoided as such treatment puts them at a higher risk for skin cancer.[12]

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.

Radiology's 'clinical value element' is tightly linked to the technology (for example, MRI as a technology is superior in soft tissue detection vs bone), but this is not the case for NGS. NGS' 'clinical value element' is not fundamentally different from that of other sequencing technologies, such as Sanger sequencing. In genomics, the 'clinical value element' is the biomarker itself. Durable and clinically meaningful coverage decisions based upon the 'clinical value element' are ideal. For NGS, the existing coverage decision based upon the *technology* is a fundamentally flawed construct, which is now 'symptomatic' as demonstrated by the need for a limited reconsideration of the NCD within 18 months of release. Further, we predict that reconsideration of this NCD will be a recurring event as medical knowledge continues to evolve and CMS continues to evaluate the NGS-based technology. AMP is very concerned that the challenges created by this policy and the need for regular reconsideration will stifle innovation contrary to the stated goals of CMS Administrator Verma.

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[9] American Society of Breast Surgeons Consensus Guideline on Genetic Testing for Hereditary Breast Cancer (2019).
[10] Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017:130:e110–26.
[11] Nandikolla, A. et al. Breast cancer in patients with Li–Fraumeni syndrome – a case-series study and review of literature Breast Cancer (Dove Med Press). 2017; 9: 207–215. Accessed at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5367777/.
[12] NCCN Guidelines for Patients: Squamous Cell Cancer 2019. Version 2.2019. Accessed at: https://www.nccn.org/patients/guidelines/squamous_cell/19/.

While we recognize there may not be an opportunity to redesign the NCD based on the biomarker and to be agnostic to sequencing methodology, AMP strongly encourages CMS to adopt this approach going forward. Moreover, evidence-based guidelines from the NCCN, American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), AMP, CAP, and World Health Organization (WHO) support the clinical utility of molecular alterations in various diseases but do not specify the technologies utilized to detect those methods. These guidelines recognize that such alterations can also be detected by other non-NGS technologies, and as such, coverage policy should not be restricted to a specific method, but to the genetic alteration(s), cancer type, and targeted therapy combination that together defines clinical relevance.

To conclude, clinical utility for germline-only NGS-based tests in Medicare beneficiaries with early stage cancer exists in multiple forms, from selection of various treatments including targeted therapy or chemotherapy treatment, avoidance of certain treatments (contraindications), to determination of appropriate surgery options and disease monitoring. AMP recommends[13] that if CMS is prohibited from excluding all non-advanced NGS-based germline testing as described, that CMS should allow coverage for NGS-based germline testing for non-advanced cancers to be at the discretion of the MACs.

Thank you again for the opportunity to provide input on the NCD. We look forward to working with you during this process to provide evidence and expert opinion on cancer testing and we appreciate CMS' willingness to engage with AMP and the laboratory community on the matter. If you have any questions, please contact Tara Burke at tburke@amp.org.

Sincerely,

Victoria M. Pratt, PhD, FACMG
President, Association for Molecular Pathology