May 28, 2019

Tamara Syrek Jensen, JD
Director, Coverage & Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
Mailstop S3-02-01
7500 Security Blvd
Baltimore MD 21244

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

Dear Ms. Syrek Jensen:

The Advanced Medical Technology Association (AdvaMed) and AdvaMedDx commend the Centers for Medicare & Medicaid Services’ (CMS) on its decision to reopen the National Coverage Determination (NCD) for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer.\(^1\) We are pleased to offer the following comments and look forward to providing more detailed comments on the proposed Coverage Decision Memorandum when it is released later this year.

AdvaMed member companies produce the medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMedDx functions as an association within AdvaMed and its member companies produce advanced \textit{in vitro} diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and often reduce overall health care costs. Our membership includes manufacturers engaged in the development of innovative diagnostics that support the advancement of public health, including next generation sequencing-based technologies. Throughout this letter, AdvaMed refers to both AdvaMed and AdvaMedDx.

\textit{Comments on Reopening of NGS NCD}

We appreciate the opportunity to provide comments as CMS considers ways to improve the existing NCD. While we applaud CMS for moving to establish national coverage for certain NGS applications upon FDA clearance or approval of related tests, we also recognize that there

is still significant uncertainty related to the implementation of the NCD. We look forward to working with the Agency and our member companies to reduce that uncertainty and ensure new technologies are available to Medicare beneficiaries who need them.

AdvaMed has long supported the use of valid evidence to inform medical care. Companion diagnostic tests play a critical public health role in supporting the safe and effective use of therapeutic products. We support access to these important tests that play an integral role in personalized medicine.

NGS is a tool that can be used for many applications, from hematology/oncology to immunology and more. We support creating a rational path to coverage for additional uses of NGS (such as initial diagnostic assessment, tracking diseases longitudinally, or where companion designation of a test is not plausible) in the hope that patient access to new NGS-based tests will keep pace with the development of clinical utility evidence.

**Application to Testing for Germline Mutations and Hereditary Cancers**

We appreciate CMS’s recognition of this important technology for tests indicated for use with patients with advanced cancer, and we support CMS’s decision to reconsider the evidence available for germline mutation testing to identify patients with inherited cancers who may benefit from targeted treatments based on the test results. For inherited diseases, testing for germline mutations may include targeted panels, whole exome and genome or mitochondrial DNA testing.

Unlike single biomarker testing, NGS can cost-effectively review samples across larger panels through use one test. NGS has been validated through applications such as breast cancer. Nicolussi, et al (2019)\(^3\) reported 100% concordance of NGS for BRCA 1 and 2 testing compared with Sanger sequencing. Authors reported high sensitivity, ease of use, turnaround time and lower cost as motivators for use NGS testing methods.

In 2017, Pearlman, et al\(^4\) found individuals with Lynch Syndrome are 15x more likely to meet Amsterdam criteria and >5x more likely to have cancers as compared with those with double

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somatic tumours. Researchers tested DNA for 25 cancer mutations susceptibility genes using NGS. Of the 450 subjects tested, 72 (16%) had gene mutations. NGS testing enabled early detection and treatment of CRC.

More recently, Christakis (2019)\(^5\) and his colleagues described the accuracy of NGS testing and recommended use in first line screening to detect microsatellite instability and screening for Lynch syndrome for colorectal cancer. Evaluating a cohort of 645 subjects, researchers found sequencing methods had identified microsatellite instability in 3.6% (23 of 645) of upper gastrointestinal tract cancers, including 28% (8 of 29) of small intestinal and 9% (9 of 97) of gastric carcinomas. In 20 cancers classified as having microsatellite instability, 19 demonstrated loss of expression of MLH1, PMS2, MSH2, or MSH6, and one cancer was indeterminate by immunohistochemistry. In contrast, 52 control cancers demonstrated retained expression of all mismatch repair proteins. Using targeted sequencing as the initial screening test, 1.1% (7 of 645) of patients was identified to have pathogenic germline variants confirming a diagnosis of Lynch syndrome.

Moreover, the NCCN Guidelines endorse germline testing for management (as opposed to targeted treatment) of early-stage hereditary cancer syndromes like thyroid cancer. Notably, neither the literature nor the guidelines distinguish between testing performed on an NGS platform versus testing using other sequencing methods, such as Sanger sequencing, which can lead to disparate coverage policies for the same type of testing when performed on different platforms.

Use of NGS technology for germline testing is critically important as it enables earlier detection and treatment, lowers overall cost and encourages individualized care for Medicare beneficiaries.

**Application to Testing for Early Stage Cancers and Treatment Monitoring**

When CMS issued the proposed NCD in 2017, we noted our concern that the way CMS defined “advanced cancer” could inappropriately narrow coverage for FDA cleared or approved NGS-based companion diagnostics for some patients, given many NGS-based tests are indicated to aid

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in identifying patients who are eligible for targeted therapies regardless of the stage of cancer and/or recurrence.

CMS’s interpretation of the NCD prohibits the coverage of NGS-based testing for patients with earlier stage cancer and testing that requires repeated use of the test over time, such as identifying minimal residual disease. The NCD should not become a barrier to future developments in the field. CMS should clarify that coverage also would apply when consistent with approved companion diagnostic tests so that coverage would not be foreclosed, for example, for a patient with early stage cancer, when consistent with the FDA cleared or approved test.

We urge CMS to consider implementing a flexible approach to coverage through national coverage or MAC discretion that provides clinicians and their patients access to a valuable tool as evidence is generated for new clinical uses. Such an approach should preserve the ability to establish new policies that are supported by clinical evidence and are consistent with the March 2018 NCD. Importantly, this would safeguard existing coverage policies that predated the NCD and allow MACs the discretion to maintain existing coverage policies for early-stage cancer testing, providing beneficiaries access to important therapies that may well be indicated at an earlier cancer stage.

Thank you for the opportunity to provide these comments. Please feel free to contact me at cbranham@advamed.org if you have any questions concerning these comments.

Sincerely,

Chandra N. Branham, JD
Vice President, Payment & Health Care Delivery Policy
AdvaMed