May 29, 2019

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

Dear Ms. Jensen,

Friends of Cancer Research (*Friends*) is an advocacy organization based in Washington, DC that drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients. During the past 20 years, *Friends* has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible.

Next Generation Sequencing (NGS) is a powerful laboratory approach which represents a new gold standard for genetic testing in cancer. While there are many diagnostic techniques used in oncology, including immunohistochemistry, in situ hybridization, and polymerase chain reaction, NGS provides the most comprehensive genetic analysis of a patient’s cancer because it enables simultaneous collection of multiple clinically relevant genetic alterations. This approach can elucidate clinically actionable information in cancers to help guide patients and physicians as they develop a treatment strategy.

In comments offered on the Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N), *Friends* commended the recognition by CMS of the importance of NGS tests and its intent to ensure uniform coverage of and beneficiary access to NGS-based tests with demonstration of analytical and clinical validity. However, the National Coverage Determination (NCD) was finalized with substantial changes that we believe undermined the intent of the policy to protect patients from unvalidated tests and, under certain circumstances, restrict access for patients to the most appropriate diagnostic tests available. Therefore, we support the Coverage and Analysis Group’s decision to open the National Coverage Analysis (NCA) for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R) for

---

**Further Consideration of Available Evidence.** We welcome the opportunity to provide more input on coverage policy for NGS tests to ensure that patients receive high-quality diagnostic testing that provides accurate information to guide treatment selection.

**Scope of the National Coverage Assessment**

NGS tests are covered nationally, as described in the Medicare National Coverage Determinations Manual², when “performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, when ordered by a treating physician,” and when other criteria are met including: the patient has either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer and has “either not been previously tested using the same NGS test for the same primary diagnosis of cancer, or repeat testing using the same NGS tests only when a new primary cancer diagnosis is made by the treating physician”. It is further stipulated that the NGS-based tests must be an FDA-approved or cleared companion diagnostic used for an FDA-approved or cleared indication.

There are key aspects of this coverage policy that we hope can be evaluated within the scope of this NCA and reconsidered for coverage in the proposed NCD to be published on or before October 29, 2019.

**Frontline Therapies**

The Medicare National Coverage Determinations Manual limits coverage of NGS-based tests when used for patients with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer based upon an extensive review of clinical outcomes in clinical trials for NGS tests. *Friends* is concerned that isolating coverage to these patients will restrict access of patients with early stage or an initial diagnosis to NGS tests. As noted on page 66 of the Proposed Decision Memo (CAG-00450N)³, there is some evidence that the composition of genetic alterations in recurrent and advanced stage IV cancers may have accumulated in response to initial radiation or chemotherapy.⁴,⁵ This may hinder a patient’s ability to receive the targeted treatment most appropriate to the genetic makeup of the individual’s cancer. **CMS should reconsider the evidence supporting expanded coverage of NGS-based testing for earlier stage diagnosis in addition to recurrent, metastatic, and advanced stage IV cancers in this NCA to ensure all patients receive the most efficacious treatment.**

---

Repeat Testing
Monitoring of minimal residual disease (MRD) is an important component of oncology care and the first NGS-based test to evaluate MRD has now been authorized by the FDA. There are now several FDA drug labels that incorporate MRD data/evaluation across a range of hematologic cancers.

Ultimately, monitoring may prove useful in solid tumors as well, with development of improved diagnostics for circulating tumor DNA (ctDNA) detected in blood samples. The utility of MRD/monitoring diagnostic tests will be hampered, however, if coverage is limited to single testing, disincentivizing innovation of these tests, and hindering patient access to appropriate treatments. We urge CMS to remove the restriction for coverage of repeat testing when necessary for clinical care.

Germline Testing
Clarification regarding the scope of this NCA (CAG-00450R) is necessary. We note that the NCA will apply to the benefit category “diagnostic tests (other),” established under Chapter 15, Section 10 of the Medicare Benefits Policy Manual. However, Medicare benefits are subject to Sec. 1862 (1)(A) of the Social Security Act, which limits the scope of Medicare coverage “except for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member”. We interpret this to mean that genetic screening tests to determine risk of disease do not fall within the “diagnostic tests (other)” benefit category. Therefore, this NCA will consider evidence regarding use of NGS-based tests to detect germline mutations for diagnosis and treatment of cancer and will not address NGS-based tests for screening of germline mutations. In other words, NGS tests to detect germline mutations in individuals without cancer is not affected by current coverage policy established by the NCD (CAG-00450N) or this NCA (CAG-00450R) and continue to be subject to regulations for the “preventable services” benefit category. We fully support evaluating evidence related to germline sequencing for cancer diagnostic and treatment indications and reconsideration proposed in this NCA (CAG-00450R). We request clarification regarding whether NGS-based tests for screening of individuals to determine cancer risk is non-covered under current coverage policy, NCD (CAG-00450N), or if new evidence supporting coverage of NGS tests for screening cancer risk can be considered under this NCA.

Narrowing Non-Coverage
Friends is concerned that, under current coverage policy, all NGS tests are considered in scope and subject to the strict criteria of either national coverage (only FDA-approved or cleared companion diagnostics) or Medicare Advantage Contractor (MAC) discretion (which is restricted by certain criteria outlined in the Medicare Benefit Manual). All other tests that do not meet those criteria, such as tests for early stage cancer detection, repeated tests for disease monitoring, or new biomarkers, are non-covered and would require a re-opening of the NCD to obtain coverage. Given the fast pace of discovery in oncology and rapid innovation of NGS tests, the requirement to issue a new NCD for expanded coverage will quickly pose an unnecessary and excessive burden for both CMS and the industry. We urge

---

8 For example, Blincyto: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-blinatumomab-blincyto-amgen-inc-treatment-adult-and-pediatric
9 SSA Sec. 1862 (1)(A)
CMS to consider a significantly less restrictive national non-coverage policy that will enable expansion of coverage to new NGS tests as they become available while maintaining consistent patient access.

Supporting Innovation of Next-Generation Sequencing

NGS technology is an area of rapid innovation particularly in oncology where new biomarkers and targeted therapies are increasing demand for high quality and efficient sequencing platforms. These tests, because they enable testing of the entire cell genome for multiple genetic alterations simultaneously, are highly amenable to modifications that improve and expand on current capabilities. Thus, it is imperative that coverage policies are adaptable to expand coverage for test modifications and expansions of use to facilitate continued innovation as new evidence becomes available.

CMS acknowledged the importance of developing evidence in the previous proposed NCD in which coverage with evidence development (CED) was proposed. CED is a mechanism that CMS has used previously to provide patient access to innovative technologies while the evidence needed to support coverage was being developed. *Friends* expressed appreciation for this intent in public comments to CMS at the time but also recognized that, while CED may be a successful model when applied to other innovative technologies, CED was not an appropriate mechanism for evidence generation for NGS tests because of the unique regulatory landscape that exists. Further, academic laboratories have been the principal drivers of innovation of NGS tests, and necessitating reporting to registries or enrollment in clinical trials as a requirement for coverage would place undue burden on academic test developers and negatively impact the fast pace of innovation for NGS tests. We agreed with the decision of CMS not to require CED; however, we believe that the final coverage policy is equally problematic as it leaves coverage of a substantial number of tests to MAC discretion with no consistency for patient access. In the interest of promoting innovation, *Friends* encourages CMS to consider a framework for coverage of NGS-based tests that is both flexible and evidence-based but that is not overly burdensome to test developers.

A framework for coverage of NGS-based tests should exhibit the following general criteria:

1. Provides national coverage to ensure consistent patient access.
2. Is flexible to evolve as technology evolves.
3. Does not pose overly burdensome reporting requirements on test developers.
4. Provides a pathway to full coverage through generation and transparency of evidence.

The ideal coverage policy should balance rigorous requirements for demonstration of analytical and clinical validity with continual evaluation of evidence as tests are improved and expanded. Given the differential regulatory landscape for diagnostic tests, where manufacturer-developed tests are reviewed by FDA and clinical laboratories are not regularly subject to FDA oversight, coverage should not be biased to consider only those tests that undergo FDA review. Certainly, we appreciate the level of evidence required for FDA approval or clearance and the contribution of clinical utility which the required clinical trials can provide, and favor the development of a more uniform regulation of tests. However, a stringent requirement for numerous tests with the same intended use and methodology (NGS) to demonstrate clinical utility in a serial fashion may not be feasible. Therefore, where clinical validity and/or utility of an FDA-approved or cleared NGS test exists to identify a biomarker of well characterized significance, other sources for demonstration of equivalent analytical and clinical
validation should be explored. For example, the FDA has acknowledged the high level of rigor that New York State Department of Health (NYS) requires in its reviews of NGS tests and has certified NYS as a third-party reviewer for diagnostic tests. Further, current policy already requires laboratory CLIA certification for coverage of a NGS-based test and CMS accepts laboratory inspections by the College of American Pathologies (CAP) in lieu of CMS inspections. Although CLIA and CAP certification are only reported at the level of laboratory certification, both also require validation of individual tests\(^1\). If a greater level of transparency could be achieved, for example, an individual laboratory or CLIA itself could report certification of analytical validation for each NGS-based test, this could provide greater confidence in the quality of the test to CMS and patients to support coverage. We suggest that CMS expand coverage to include, where an FDA-approved or cleared NGS test already exists, NGS tests that demonstrate adequate analytical and clinical validity as compared to an existing approved or cleared NGS test through a certified third party—with increased transparency of CAP/CLIA evaluations that can be elevated to the provide information at the level of each variant of significance on a NGS test.

Since laboratories are already subject to thorough proficiency evaluation and test analytical validation with extensive local documentation by CLIA, the requirement to report certification, or even the parameters of certification, on each NGS test would not create overly burdensome requirements for test developments. Further, as academic labs are major drivers of innovation in NGS-based testing, expanding coverage to tests through third-party review could provide a feasible pathway to coverage with evidence generation. For example, CMS could consider adapting the Appropriate Use Criteria (AUC) framework\(^1\), which CMS has been statutorily required to implement for determining appropriate uses to merit reimbursement for advanced diagnostic imaging tests, to enable continual evidence evaluation for NGS tests to inform coverage. Since CMS already has experience implementing AUC for reimbursement, a similar framework to inform ongoing assessment of coverage, appropriate use for coverage, could be implemented under CMS’ authority to require evidence generation. As with the existing AUC Program, entities with expertise in diagnostic and clinical assessments could be identified for certification as Provider Led Entities (PLE). These PLEs would be qualified to develop, modify, and endorse AUC based on the submissions of a minimum set of analytical and clinical validation elements, which could include data sourced from real-world evidence, necessary to support determinations of coverage for diagnostic tests. Certain real-world endpoints, when well-defined and standardized, have been shown to be readily extractable from electronic health records and claims-based databases and relevant to clinical trial endpoints for anti-PD-(L)1 therapies\(^2\). An AUC-like framework, if adapted to NGS tests, would enable ongoing assessment of current NGS technology and validation standards. Further, as NGS tests evolve and become increasingly sensitive and accurate, PLEs could raise validation requirements for NGS tests that must be met to qualify for coverage. This would create a coverage policy that could evolve over time along with NGS technology.

\(^{10}\) 42 CFR § 493.1253  
\(^{11}\) 42 C.F.R. § 414.94  
Conclusion

We hope that CMS will consider the recommendations made in this document and look forward to further inform discussions with the agency.

Sincerely,

Jeff Allen, PhD
President & CEO
Friends of Cancer Research