January 17, 2018

Seema Verma, Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Email: Seema.Verma@cms.hhs.gov; CAGinquiries@cms.hhs.gov

RE: Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N)

Dear Ms. Verma:

On behalf of Facing Our Risk of Cancer Empowered (FORCE) and Living Beyond Breast Cancer, we are pleased to submit the following comments regarding the proposed National Coverage Determination (NCD) "Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer."

We support the Food and Drug Administration (FDA) and Centers for Medicare and Medicare Services (CMS) Parallel Review program to streamline approval and coverage processes. We also applaud the CMS for recognizing the value of precision oncology diagnostics in the care of cancer patients. Our organizations agree that a positive coverage determination for coverage of FoundationOne CDx (F1CDx) is in the best interest of the Medicare population.

The proposed NCD, however, goes well beyond coverage of one test. It strives to establish a broad policy for coverage of all NGS-based tests. As such, it warrants close scrutiny. NGS testing is very complex. We support validating any test that impacts patient care to ensure safety, efficacy, validity and quality. Given that our organizations place a heavy emphasis on serving and supporting the patient population, our comments focus on access to care and the components of the policy that we are most qualified to address.

Coverage Clarifications

Stage: The proposed policy stipulates that the patient has "recurrent, metastatic, or advanced stage IV cancer." Because certain cancers are referred to by the stage it was given at diagnosis, a stage III cancer may eventually become metastatic although it would remain a stage III diagnosis. Would these patients qualify for coverage based on the proposed

NCD? We urge CMS to further elucidate these parameters to ensure that the greatest number of patients have access to the benefits of NGS testing.

Prior Testing:
The memo states that the patient qualifies for coverage if s/he has "not been previously tested using the same NGS test." It is now understood that only a small proportion of the cancer cells that leave a tumor succeed at metastasizing to a distant organ. Importantly, metastatic cancers change genetically due to the natural progression of disease or in response to previous anti-cancer treatments. Even within single primary tumors there can be considerable genetic mutation heterogeneity (1). Consider the example of a resistance mutation that may be limited to one or a few loci: resistance to EGFR targeted therapies in cancer very frequently involves a single point mutation, and can possibly be overcome by merely switching to a different agent (2). Thus, we believe that limiting coverage to patients who have not previously tested using the same NGS test is a short-sighted approach. It is likely that many patients who were previously tested and whose cancer has genetically changed over time may benefit from additional testing—even with the "same NGS test." We ask CMS to reconsider the coverage criteria to allow the use of NGS testing more than once to identify new mutations that may develop or be revealed during disease progression as these newly identified genomic changes may guide additional treatment.

Coverage in Earlier Cancer Settings
Personalized medicine should not be reserved for only those who have advanced or metastatic disease. The goal is to prevent cancer altogether, or to stop early stage disease from advancing. In colorectal cancer, for instance, there is considerable stage-independent variability in clinical outcomes. This variability underscores the need for prognostic and predictive biomarkers to guide therapeutic decision-making. Consequently, many colorectal cancer patients benefit from microsatellite instability testing before the cancer is advanced or metastatic. In the case of prostate cancer, the germline component to clinical NGS testing may have significant diagnostic and therapeutic utility, as demonstrated by the identification of pathogenic germline alterations in men with castration-resistant prostate cancer who respond to PARP inhibition (3). Or, the observation that many breast and prostate tumors in non-germline mutation carriers have tumors with BRCA-like features. These tumors may respond well to PARP inhibitors in the early cancer setting (4). We encourage CMS to explore the viability and utility of NGS testing in earlier cancer settings. This will serve the Medicare system by saving money on unnecessary or ineffective therapies, and the patient population by identifying the best treatment for each patient regardless of disease stage.

Coverage with Evidence Development
While the impetus for this NCD is parallel review and coverage of FoundationOne CDx, its scope goes far beyond one test. In fact, the proposed memo may be interpreted as a sweeping policy that could eliminate Medicare coverage for other types of genetic testing, both in oncology and in non-cancer indications. This is of great concern. The proposed NCD provides coverage with evidence development (CED) for FDA cleared or approved tests that are used in NCI approved clinical trials. The criteria in the CED section is very restrictive. It appears that most clinical genetic tests used today would not be eligible for

coverage through this process. For instance, if the policy is broadly applied, BRCA genetic testing for women with a strong family history of breast or ovarian cancer would not be covered by Medicare unless it is provided through an FDA-approved companion diagnostic test or via a research study. Perhaps this is not the intent of the proposed policy but anything that may restrict patient access to potentially lifesaving tests raises concern for our organizations. We urge CMS to closely review the potential implications of this memo to ensure that it does not have broad repercussions for the patient community in regard to access to care and the potential benefits of precision medicine.

If the CED section is interpreted more narrowly, we believe the requirements are too burdensome, and will ultimately hinder timely use of NGS services to achieve the best health outcomes. The CED section requires that, "The patient is enrolled in, and the furnishing laboratory is participating in, a prospective registry that consecutively enrolls patients, adheres to the standards of scientific integrity and relevance to the Medicare population." Theoretically, this seems reasonable but what if a registry does not exist for a specific cancer or tumor type? How will these patients gain access to the potential benefits of NGS testing? Additionally, reliance on RECIST criteria is problematic as this only applies to solid tumors. A large number of patients will be excluded from coverage if RECIST criteria is used. We understand and agree with the concept of collecting robust data that will inform the use of NGS to guide treatment decisions but with only 3% of cancer patients participating in clinical trials (less in Medicare population), CMS would be better served by reducing the burdens on patients and providers to improve participation and access to NGS testing. This might include review of the costs associated with participation, alternative methods of data collection (i.e. retrospective collection of data via chart audits and claims analyses), etc.

Beyond Tumor Testing

One area not addressed in this proposed policy is the broader possibilities and implications of genetic testing in oncology settings. There is definitely value in screening for genetic features in tumors to help guide treatment decisions but the promise of genetic testing and precision medicine is the ability to prevent cancer, or to diagnose it at an earlier stage when it is easier to treat. Tumor testing increases the opportunity to identify those with germline mutations, who may be at increased risk of other cancers, and whose results may inform family members of their potential increased risk of cancer. For example, tumor testing in 560 breast cancers revealed 33 patients with inherited BRCA mutations who did not know their status prior to the study (4). Ideally, all labs would be able to differentiate between somatic and germline mutations—and would report germline mutations found along with somatic mutations. This may not be feasible, however, so we suggest that CMS institute a policy on lab reporting of possible germline mutation findings. For example, for labs doing NGS testing where a germline mutation may be identified, CMS might stipulate that they meet one of the following requirements:

A. Labs with germline testing capabilities: Incorporate germline testing into the informed consent and reporting. Therefore, potential germline findings can be validated via a blood draw, saliva test, or pathology specimen to confirm or deny the germline status.

B. Labs without germline testing capabilities: Add reporting of suspected germline mutations, the significance of these gene alternations for the patient and family members, and the recommendation of additional genetic counseling and/or germline testing.

This fits within current Medicare policies on germline genetic testing as it only impacts individuals who have already been diagnosed with cancer. It would identify Medicare beneficiaries who may be more closely monitored for second primary cancers commonly associated with the identified germline mutation. Beyond Medicare, this would serve the broader good by facilitating cascade testing—providing useful information to family members who may also carry germline mutations.

Communication

CMS asked "how can the information in this proposed NCD be clearly communicated to health care practitioners, patients, and their caregivers…?" We believe that it is crucial to develop health care provider and patient-facing materials explaining the nuances of the policy regarding the testing itself, coverage for Medicare beneficiaries, etc. Beyond the traditional Medicare communication channels, it would be wise for CMS to work with patient and health care professional organizations to disseminate the information in a variety of formats which may include web-based content, a flyer, pamphlet or brochure available in PDF format for download and printing, and infomercials or webinars for specific patient and provider populations.

In summary, we support a positive coverage determination for FoundationOne CDx (F1CDx). However, we have significant concerns regarding the broader implications of the NCD, especially the Coverage with Evidence Development policy as outlined. As such, we do not believe the NCD should be approved and finalized without significant revisions. A thoughtful, measured approach must be taken when contemplating policies that have the potential to broadly impact the patient community and its access to care. The NCD must be carefully crafted to account for new tests that come to market as well as new indications for existing tests and therapies. Can the policy easily evolve? Will it serve the needs of the community now and in the future? We urge CMS to work with industry and patient groups to develop its policies and programs related to molecular and genetic testing—and find workable solutions for all parties involved.

Thank you for you for the opportunity to contribute to this important discussion.

Sincerely,

Lisa Schlager
Vice President, Public Policy
FORCE: Facing Our Risk of Cancer Empowered

Jean Sachs, MSS, MLSP
Chief Executive Officer
Living Beyond Breast Cancer

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FORCE: Facing Our Risk of Cancer Empowered is the only national nonprofit organization representing people and families affected by hereditary breast, ovarian cancer, and related cancers. FORCE programs provide education, support, advocacy and research to empower those affected by hereditary cancer to make informed decisions about their health, including decisions surrounding genetic counseling and testing.

Living Beyond Breast Cancer (LBBC), founded in 1991, is a national nonprofit education and support organization serving women and families affected by breast cancer. LBBC's mission is to connect people impacted by breast cancer with trusted information and a community of support.

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2. Jänne PA, Yang JC-H, Kim D-W, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372:1689–99
3. Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015; 161:1215–28.
4. Davies H, Glodzik D, Morganella S, et al. "HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures." Nature Medicine. 2017; 23(4): 517-525.