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Organization: PierianDx Inc.
Date: 12/31/2017
Comment: Commenters: Rakesh Nagarajan, M.D., PH.D., Shalini Verma M.D., FCAP

Rakesh Nagarajan, M.D., PH.D.
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- Adjunct Associate Professor, Department of Pathology & Immunology, Washington University School of Medicine
- Member, Molecular Oncology Committee, College of American Pathologists (CAP)
- Member, Next-Generation Sequencing (NGS) Project Team, College of American Pathologists (CAP)
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Shalini Verma M.D., FCAP
Title: Laboratory Director and Medical Director, PierianDx Inc.

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

On behalf of PierianDx Inc. we thank CMS for the opportunity to comment on the proposed NCD. Rakesh Nagarajan is a physician-scientist with experience in molecular biology, molecular laboratory workflows and techniques and expertise in multiple informatics subspecialties including bioinformatics, clinical trials informatics, and medical informatics.

Rakesh serves as an Adjunct Associate Professor at the Washington University School of Medicine Department of Pathology & Immunology. He also currently serves on the College of American Pathologists (CAP) Molecular Oncology Committee, Genomic Medicine Resource Committee, and the Next-Generation Sequencing (NGS) Project Team, and is a molecular pathology specialty inspector for the CAP. In his role with CAP, he works with the committee to set regulatory standards through NGS checklist items for the analytic wet bench process and for bioinformatics or "dry bench" analyses for NGS-based laboratory developed tests (LDTs) and to design, develop, and monitor proficiency testing (PT). These standards and NGS checklist items address documentation, validation, quality assurance, confirmatory testing, exception logs, monitoring of upgrades, variant interpretation and reporting, incidental findings, data storage, version traceability, and data transfer confidentiality for NGS-based LDTs in a CLIA certified CAP accredited laboratory. Over the years the CAP laboratory standards for next-generation sequencing clinical tests have facilitated an appropriate adoption of NGS technology for clinical testing.

Rakesh is the founder and the Chief Executive Officer at PierianDx Inc. PierianDx solves the problem of translating complex genomic data of clinical laboratory developed NGS tests into actionable clinical insight to advance precision medicine. This is accomplished through a cloud-based clinical genomics software platform (Clinical Genomicist Workspace) that simplifies the process of taking DNA sequencing data though analysis, annotation, interpretation, final clinical report editing, and integration in the electronic health record (EHR). PierianDx serves a number of CLIA certified CAP accredited laboratories in health systems, children's hospitals, comprehensive cancer centers, and reference clinical laboratories across the United States.

Shalini Verma is a board-certified Anatomic and Clinical Pathologist with subspecialty expertise and board certifications in Hematopathology and Molecular Genetic Pathology. She trained at Los Angeles County/University of Southern California Medical Center, Los Angeles, Weill Cornell Medical College/ New York Presbyterian Hospital, New York and at The University of Texas M.D. Anderson Cancer Center, Houston. Post training she has served as Senior Medical Director and Clinical Laboratory Director at various large clinical laboratories and diagnostic companies including GE-Clarient Diagnostic Services, Roche Molecular Systems and Roche Sequencing Services. In these roles, she was responsible for providing medical oversight to the molecular diagnostic services in Clinical and the Biopharma laboratory. She has worked closely with the R&D and commercial teams to develop and better align the company/ laboratory's molecular services with the market needs. Currently, she is the Laboratory Director and Medical Director at PierianDx Clinical Laboratory.

Clinical laboratory developed NGS tests offered by CLIA certified laboratories in our client health systems, hospitals, cancer centers and, reference clinical laboratories across the United States serve millions of cancer patients including Medicare beneficiaries. Our clients have developed these NGS tests in consultation with medical experts including oncologists, molecular pathologists, and clinical geneticists who are members of many national and international professional societies, disease guidelines committees, and panels including the national comprehensive cancer center network (NCCN). These clinical NGS tests analyze clinical biomarkers which have diagnostic, prognostic and/ or therapeutic significance. Further the results of these tests may guide a patient to the appropriate standard-of-care approved medications (including FDA approved therapy), clinical trials, or assist in determining the cancer diagnosis or prognosis thus enabling personalized cancer care.

We commend CMS for their recognition of the value of precision oncology diagnostics in the care of advanced stage cancer patients as evidenced by the proposed National Coverage Determination (NCD) on clinical NGS tests. However, we believe that the proposed coverage policy is unreasonably restrictive and is likely to be disadvantageous to patient care. We share our concerns with the proposed NCD below.

- The proposal to limit the coverage only to FDA approved NGS tests with companion diagnostic indications, imposes restrictive criteria for coverage with evidence development. This also makes explicit a policy of non-coverage for NGS tests if the test does not meet the criteria listed in the proposed NCD.

- At a time when most of our client academic centers, leading cancer institutions, and essential community cancer centers have Clinical Laboratories Improvement Amendment (CLIA) certified laboratories providing validated laboratory developed NGS-based tests, the policy as proposed

would supersede existing local coverage policies for most of those tests and limit Medicare beneficiaries' access to a single test.

- We agree that the FDA approved tests have clinical utility for certain indications, but FDA approved tests are not the only clinically acceptable tests for patients with advanced cancer, nor are they the only tests that have been demonstrated to be of high quality by peer review and offered with existing regulatory oversight, e.g., the CLIA and CAP laboratory inspection processes. Re: "The Case for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care in Academic Pathology" (http://journals.sagepub.com/doi/10.1177/2374289517708309)

- The proposed NCD, if finalized, will eliminate coverage for other NGS tests for advanced cancer patients enrolled in Medicare. These tests are currently being used to deliver high-quality, advanced cancer care across the country, including at virtually all major National Cancer Institute-designated cancer centers and academic institutions and reference laboratories.

- Cancer is an evolving and a systemic disease. The accumulation of oncogenic alterations in a cancer-originating cell may set the course to malignancy, but tumor cells continue to change and evolve in order to survive, grow, and metastasize. The intratumoral diversity and clonal evolution in cancer is accompanied by change (acquisition and loss) in genetic alterations over the course of disease. The NCD proposal for coverage of the NGS test cost only one time in patient's lifetime that too at the stage of advanced cancer, severely limits a cancer patient's care.

    - "NGS test once per cancer" proposal shakes the very foundation of personalized health care and outright refuses the possibility and opportunity of monitoring cancer patients' responses to therapy both during treatment and after it is completed.
    - This proposal, if finalized, will also prevent early stage cancer patients from having access to any clinical management option that requires knowledge of NGS based genetic results in patient tumors. If testing is performed only when the disease has advanced to late stages or has severely metastasized, the patient may have missed the opportunity for life-saving therapy when the cancer was smaller, less advanced and easier to treat. This will clearly harm a majority of patients with cancer.
    - Clinical NGS testing is not just indicated for those patients who desire to seek further treatment. Cancer genetic alterations determined by NGS testing can have significance for determination of diagnosis which then informs the best course of therapy. Genetic alterations also have significance in determination of prognosis in certain cancers which have therapeutic and life-planning impact for patients.

- Precision oncology is a medical practice that occurs at the local level, at the patient's bedside and in interactions between local healthcare professionals including molecular pathologists. Clinical NGS results for our patients are personalized in the context of their respective clinical and pathological findings. Further, the flexibility to triage urgent patient samples, to discuss in depth the findings at local molecular tumor boards with a multidisciplinary team, and to participate in quality improvement initiatives specific to institutions will all be lost if testing is effectively centralized to one lab by the NCD as written.

- CMS coverage policy for Medicare beneficiaries should not exclude entire categories of testing, i.e., those that use NGS technology, when such testing is performed in CLIA accredited laboratories and adheres to evidence-based guidelines developed by leading scientists and subject matter experts and endorsed by medicine's preeminent professional societies, including AMP, CAP, ASCO, ASH, WHO, and NCCN.

- As currently proposed in the NCD, the FDA-approval requirement prevents laboratories from being able to quickly respond as new molecular alterations become clinically actionable and molecular technology improves.

- FDA oversight is not compatible with a rapidly evolving landscape. The FDA-approval process is very long, burdensome and doesn't make provisions for quick and effective updates to tests when technology updates or when new clinical information emerges. Requiring FDA approval will cause many laboratories to cease testing, reduce competition, dramatically increase costs and severely limit NGS test access to the majority of patients.

- The field of molecular diagnostics is rapidly evolving and so is our knowledge of cancer genetics and genetic biomarkers. To keep up with these a laboratory needs flexibility to quickly modify and validate / re-validate NGS tests. This goal is not achievable via the long, burdensome and cost prohibitive processes as currently laid out by the FDA.

- Most of the FDA approved tests are not validated for less common sample types such as fine needle aspiration of fluids (e.g. pleural fluids). Such samples are critical in management of patients who are not fit for tissue biopsy procedures for one reason or another. The restrictive nature of disease and sample indications of FDA approved tests coupled with burdensome test upgrade processes will severely limit access to appropriate and necessary management for many cancer patients.

- Another consideration is the research evidence showing that the laboratory developed procedures in CLIA-certified laboratories have equivalent performance to FDA approved tests. Additionally, when FDA-approved test kits are used, over 60% of laboratories are modifying those tests and revalidating them as a laboratory developed procedure (Kim AS, et al. https://jamanetwork.com/journals/jamaoncology/article-abstract/2665746). This is because the constraints under which the FDA assay needs to be performed may prevent economies of scale for the volume and sample type testing that is necessary for a laboratory. The referred study here stated that 60% of the participants modified an FDA approved – companion diagnostic test to allow for a greater breadth of sample types, minimum tumor content, and instrumentation (Kim AS, et al. https://jamanetwork.com/journals/jamaoncology/article-abstract/2665746).

- The restrictive nature of the draft NCD potentially stifles innovation, a hallmark and highlight of the American healthcare system. Because NCDs are difficult to modify, in areas of rapidly advancing science they can be a barrier to advancing medical practice.

- The NCD requirement of achieving FDA approval for coverage is inconsistent with the FDA's position on enforcement discretion for laboratory developed testing procedures (LDPs) including its 2016 announcement that it does not intend to finalize the draft guidance establishing a framework to regulate LDPs. Rather, the NCD requirement of FDA approval for coverage establishes the FDA as determining the regulatory bar for acceptable clinical tests and thereby the practice of medicine. As a regulatory bar, FDA approval is impractical or impossible for most laboratories to reach, including those in many leading academic medical centers and cancer programs. Laboratories cannot sustain clinical services without reimbursement, and therefore would have to stop offering NGS-based tests to patients with advanced cancer.

- Next generation sequencing, or NGS, is a technology and is not a diagnostic test. The NCD focuses on a specific technology and is not tied either to a specific biomarker or specific CPT code. This approach runs counter to established coverage determinations, which are based on the clinical utility of a proven effective biomarker, independent of test methodology and whether a test has received regulatory approval for marketing and labeling. If finalized, it will disrupt existing local coverage policies for more targeted panels and specific CPT codes.

- The coverage with evidence development (CED) requirements within the proposed NCD are too prescriptive.

- Thank you for the opportunity to comment on this important issue. Given our expertise and experience, we would be happy to serve as a resource to CMS in this process. Please feel free to contact us for any questions about our comment or any other information that may be helpful.

Sincerely,
Rakesh Nagarajan, M.D., Ph.D.
Shalini Verma, M.D., FCAP