November 27, 2017

Part B Policy
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RE: MolDX: Circulating Tumor Cell Marker Assays (DL35071)

Dear Dr. Almas,

Thank you for the opportunity to review and comment on Palmetto's proposed coverage policy for Circulating Tumor Cell Marker Assays (DL35071). The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 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 the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the College of American Pathologists (CAP) serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

We agree with Palmetto's position that there is insufficient evidence at this time to support coverage for direct measurement of circulating tumor cells. However there is evidence that PCR (RT-PCR) assays for cell-free DNA change physician management and improve patient outcomes. Therefore, we propose one specific amendment to the policy language to clarify that circulating cell-free DNA and circulating tumor cells are not the same and that this non-coverage policy should only apply to circulating tumor cells (and not to cell-free DNA).

There is a difference between tests that have been developed for circulating tumor cells and circulating tumor DNA or cell free DNA (cfDNA). Tests based on technology such as Veridex, which attempt to isolate circulating tumor cells, have not been widely utilized clinically. In contrast, more recently developed technologies (ddPCR, NGS) have enabled testing which examines circulating tumor DNA found in plasma. This testing has been successfully used clinically in diseases such as non-small cell lung cancer (e.g., cobas® EGFR Mutation Test v2). Its application as a noninvasive test that can be used to identify newly diagnosed patients with EGFR exon19 deletion or L858R mutations and monitor disease progression for EGFR T790M mutations is becoming widely utilized clinically for therapeutic decision making. Notably, the recent MolDx article A54021 "MolDX: FDA-Approved EGFR Tests" states this is a covered test. This real-time PCR test for cell-free tumor DNA from plasma has been approved recently by the FDA, and other cfDNA applications are currently being developed to identify targeted therapy for patients ineligible for a biopsy (e.g., ALK, BRAF, KRAS, MET sensitivity/resistance mutations in lung cancer).

Unfortunately, the language that is often used to describe blood-based tests to detect circulating cancer cells (or DNA) is imprecise and people often refer to these tests as "circulating tumor cell" tests (often interchangeably used with "liquid biopsy") even though the testing target is cell-free DNA, rather than intact cells. This coverage policy should not apply in any way to plasma-based liquid biopsy tests that employ PCR (RT-PCR) to detect gene mutations in cell-free DNA, which do have proven clinical utility.

Request: Please consider amending the LCD language to exclude cfDNA tests that employ PCR (RT-PCR) and avoid referring to all of these tests as liquid biopsies or circulating tumor cell tests.

Thank you again for the opportunity to review and comment on this proposed policy. If you have any questions please direct your correspondence to Tara Burke, AMP Director of Public Policy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

Association for Molecular Pathology
College of American Pathologists

References:

Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA Analysis for Detection of the EGFR T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017;12(7):1061-1070. doi:10.1016/j.jtho.2017.04.003