Support for Therapeutic Group Labeling of Diagnostic Tests:

A Joint Position Statement of the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP)

Problem

Many modern anti-cancer therapeutics target the biology of a person's tumor (e.g., genetic mutations) or modify one's immune system to eliminate tumor cells. To leverage this type of precision medicine, diagnostic tests are necessary to determine which patients may benefit from these effective therapies. The traditional "one-drug/one-test" approach to *in vitro* companion diagnostics (or tests)[1] can add to the many toxicities (e.g., death, side effects, quality of life, time, financial burden, and other social determinants of health) that limit access to some of the most effective therapeutics available for patients. The proliferation of Food and Drug Administration (FDA) approved immune therapeutics that use the same biological target but were approved with different companion diagnostics means patients and clinicians must navigate multiple tests. Each test can require additional tissue samples, add time delays while awaiting results, and represent additional costs, sometimes linked to formulary-imposed drug access restrictions related to companion diagnostic testing. In 2020, the FDA encouraged companies to address these challenges with release of the final guidance document that clarifies opportunities for diagnostic developers to obtain a diagnostic label for a group of therapeutics that use the same biological target.[2]

Recommendations

ASCO and CAP support labeling of companion diagnostics for a therapeutic group of products, as outlined in the FDA guidance "Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products." We urge manufacturers of diagnostic and therapeutic products to follow the process outlined in the guidance to:

- Prioritize evidence development through pragmatic/decentralized trial elements to support labeling diagnostics for use in a group of oncology therapeutics, rather than labeling a companion diagnostic for a single therapeutic product within the group.

- Explore extending diagnostic labels for existing companion diagnostics to a therapeutic group of products through submission of a supplemental application. Work with the FDA to implement innovative approaches to evidence generation and regulatory flexibility, as appropriate, and

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[1] Food and Drug Administration. Companion Diagnostics. June 20, 2023. Available at www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics. Accessed December 6, 2023.

[2] Food and Drug Administration. Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products: Guidance for Industry. April 2020. Available at https://www.fda.gov/media/120340/download.

- Prioritize broadening labels of the diagnostics that guide the use of PD-(L)1 directed immune checkpoint inhibitor (ICI) therapeutics.

Background

Many cancer drugs or biologic therapies target a molecular aspect (biomarker) of the cancer cell or a person's immune response to either interrupt cancer growth or activate the immune system to eliminate cancer cells. Use of biomarker-directed therapeutics requires a diagnostic device or test to determine whether a person's tumor has the relevant biomarker and may respond to the therapy. Therapeutic manufacturers often use one or more devices/tests during clinical trials and usually submit a single device/test to the FDA as part of the application (or applications) if the diagnostic requires FDA clearance for approval. The FDA 2014 guidance on companion diagnostics states that the Agency will classify the in vitro diagnostic device/test as a companion diagnostic if it is "essential for the safe and effective use of a corresponding therapeutic product."[1] The current companion diagnostic model and formulary-imposed drug access restrictions pose challenges to achieving equitable biomarker driven care. Challenges arise if there are multiple therapeutics indicated for a disease that target the same biomarker but used different companion diagnostics for FDA approval.

Patients face this challenge in the immuno-oncology space with several FDA-approved immune checkpoint inhibitors (ICIs) that target PD-(L)1 and require multiple specific anti-PD-(L)1 companion diagnostics for their on-label/indicated use. To provide access to all indicated ICI therapies, oncologists and pathologists must run multiple diagnostic tests that target PD-(L)1. For the patient, this may result in an extended time to complete diagnosis/evaluation and additional expenses. Clinicians also are challenged in how to advise patients about issues related to tissue stewardship, as additional tissue testing may be required to treat the patient's disease. Furthermore, if the required testing platforms are not available to perform a particular companion diagnostic locally, this can contribute to delays in care and limit patient access to appropriate biomarker driven therapies. Finally, the current one drug/one test paradigm can result in financial burden to both the patient and the healthcare system as multiple tests for the same biomarker are frequently performed to be compliant.

Clinicians also are challenged by the array of companion diagnostics. If a therapeutic agent is approved on the basis of a companion diagnostic, the therapeutic label guides the prescriber to use "an FDA-approved test" for the biomarker, without naming the companion diagnostic. In contrast, the diagnostic label names the specific therapeutic product it is paired with (see Table 1). The treating oncologist may not know which companion diagnostic to order for on-label treatment or if the appropriate companion diagnostic is available at the local/preferred laboratory. Laboratories may not offer, nor have the instrumentation/methods to run, all companion diagnostics that apply for a therapeutic group. Some laboratories develop their own alternative diagnostics for certain biomarkers. Finally, payers may impose restrictions on coverage based on whether a companion diagnostic was used.

A large amount of evidence is required to support a companion diagnostic claim, and companies are not incentivized to collaborate or share data. As a result, peer-reviewed evidence and publicly available data are insufficient to demonstrate equivalency or allow harmonization among companion diagnostics for the same biomarker, further enforcing the one drug/one test paradigm. Finally, precision medicine is a fast-evolving space, and new indications for a specific therapeutic and their respective diagnostics occur frequently. Oncologists and pathologists are

challenged to remain up-to-date, particularly when a new diagnostic is required for a particular biomarker/therapeutic pairing.

The FDA recognized challenges associated with the "one drug/one test" paradigm and published a 2020 guidance that enables manufacturers to seek a diagnostic label for a group of therapeutics (e.g., anti-PDL1 or EGFR inhibitors). In effect, this guidance aligns diagnostic labeling with therapeutic labeling, enabling a diagnostic label to refer to a group of therapies, not only the specific therapeutic it was paired with at approval (e.g., 'EGFR inhibitors rather than 'erlotinib'). The table below highlights the current state (one drug/one test) and future state (therapeutic group label), demonstrating an improvement in pairing the appropriate test with the appropriate group of therapies.

Unfortunately, adoption of therapeutic group labeling for companion diagnostics has been slow.[3] According to the FDA, only four companion diagnostics have received group labeling claims as of October 5, 2023.[4] Underutilization of group labeling may relate to lack of commercial incentive, as well as additional time and expense associated with conducting the studies necessary to support a group label claim.

Conclusion

ASCO and CAP call on manufacturers of diagnostics and therapeutics alike to utilize this regulatory pathway and improve access to effective modern therapies. ASCO and CAP believe therapeutic group labeling will enhance patient access, clinical simplicity, diagnostic efficiency, and cost effectiveness for these important therapies.

Questions? Contact Suanna Bruinooge at Suanna.Bruinooge@asco.org or 571-483-1613

Table 1. Diagnostic Label Differences with Companion Diagnostic Label and Group Therapeutic Label

	Therapeutic Label	**Companion Diagnostic Label**
Current State (one drug/one test paradigm)	XXXX® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as **detected by an FDA-approved test.**	The AAAA® BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue. The AAAA®BRAF V600 Mutation Test is a real-time polymerase chain reaction (PCR)test on the AAAA® system, and is intended to be used as an aid in **selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with XXXX®**

[3] Scheerens H, Malong A, Bassett K, et al. *Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch.* Clin Transl Sci. 2017 Mar;10(2):84-92. doi: 10.1111/cts.12455.

[4] U.S. Food and Drug Administration. *List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools).* October 6, 2023. Available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Future State (Therapeutic group label paradigm)	XXXX® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as **detected by an FDA-approved test.**	The AAAA® BRAF V600 Mutation Test is an in vitro diagnostic device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue. The AAAA® BRAF V600 Mutation Test is a real-time polymerase chain reaction (PCR) test on the AAAA® system and is intended to be used as an aid in **selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with an FDA-approved BRAF inhibitor.** **List of BRAF Inhibitors approved by FDA for this indication:** **XXXX® (yyyy) – NDA ZZZZZZ** **BBBB® (cccc) – NDA FFFFFF**