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Companion Diagnostics

Lessons Learned and Path Forward From the Programmed Death Ligand-1 Rollout

Joseph E. Willis, MD; Frederick Eyerer, MD; Eric E. Walk, MD; Patricia Vasalos, BS, MT; Georganne Bradshaw, MT(ASCP); Sophia Louise Yohe, MD; Jordan S. Laser, MD

• ***Context.***—**Programmed death ligand-1 (PD-L1) immunohistochemistry companion diagnostic assays play a crucial role as predictive markers in patients being considered for immune checkpoint inhibitor therapy. However, because of a convergence of several factors, including recognition of increased types of cancers susceptible to immunotherapy, increasing numbers of immune checkpoint inhibitors, and release of multiple PD-L1 immunohistochemistry antibodies with differing reporting systems, this complex testing environment has led to significant levels of confusion for pathologists and medical oncologists.**

Objective.—**To identify which processes and procedures have contributed to the current challenges surrounding programmed death receptor-1 (PD-1)/PD-L1 companion diagnostics and to propose potential remedies to this issue. This is based upon input from key industrial stakeholders in conjunction with the College of American Pathologists Personalized Health Care Committee.**

Design.—**A meeting of representatives of pharmaceutical and in vitro diagnostic companies along with the Personalized Health Care Committee reviewed the process of release of the PD-L1 companion diagnostic assays using a modified root cause analysis format. The modified root cause analysis envisioned an ideal circumstance of development and implementation of a companion diagnostic to identify shortcomings in the rollout of the PD-L1 assay and to suggest actions to improve future companion diagnostic assay releases.**

Results.—**The group recommended improvements to key principles in companion diagnostics implementation related to multi-stakeholder communication, increased regulatory flexibility to incorporate postapproval medical knowledge, improved cross-disciplinary information exchange between medical oncology and pathology societies, and enhanced postmarket training programs.**

Conclusions.—**The rapidly changing nature and increasing complexity associated with companion diagnostics require a fundamental review of processes related to their design, implementation, and oversight.**

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In 2011, the US Food and Drug Administration (FDA) approved ipilimumab for the treatment of metastatic melanoma. This was followed by approval of several cancer immunotherapies directed against the programmed death receptor-1/ligand-1 (PD-1/PD-L1) pathways, starting with nivolumab and pembrolizumab in 2014 for treatment of metastatic melanoma. Following these earlier trials, an increasing number of cancers have been found to be susceptible to immune checkpoint inhibition[1–4] and some studies have demonstrated synergy between CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors (ICIs) in a number of cancer systems.[4–7] Conventional cancer therapies leading to tumor cell death with T-cell activation by release of tumor antigens will likely have a pivotal role in cancer checkpoint inhibitor therapies.[8] Recent data have identified a promising role for neoadjuvant checkpoint inhibitor therapy in a variety of cancers, in addition to its role in treating advanced cancer patients who have failed first-line therapy.[7,9–18] There are currently 7 ICIs approved by the FDA: ipilimumab (an anti–CTLA-4); PD-1 inhibitors nivolumab, pembrolizumab, and cemiplimab; and PD-L1 inhibitors atezolizumab, avelumab, and durvalumab.[4] These drugs, as single agents or in combination with other standard therapies or ICIs, have been approved for an increasing number of solid and hematopoietic malignancies with significant improvements in patient outcomes.[4] With further advances, the opportunities for improvements in immunotherapy concepts and therapeutics are obvious. For example,

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From the Department of Pathology, University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, Ohio (Willis); the Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, Burlington (Eyerer); Roche Diagnostics Medical and Scientific Affairs, Tucson, Arizona (Walk); Proficiency Testing, College of American Pathologists, Northfield, Illinois (Vasalos, Bradshaw); the Department of Laboratory Medicine and Pathology, M Health Fairview–University of Minnesota, Minneapolis (Yohe); and the Department of Pathology and Laboratory Medicine, Northwell Health, New Hyde Park, New York (Laser). Walk is now with the Department of Medical, Regulatory and Clinical Affairs, PathAI, Boston, Massachussets. Laser is now with Everly Health, Austin, Texas.

Walk was a former employee of Roche Diagnostics and a Roche shareholder. The other authors have no relevant financial interest in the products or companies described in this article.

All authors are current or past members of the College of American Pathologists Personalized Health Care Committee. Vasalos and Bradshaw are employees of the College of American Pathologists.

Laser is currently located at Everly Health, Austin, Texas.

Corresponding author: Jordan S. Laser, MD, Everly Health, 823 Congress Ave, Ste 1200, Austin, TX 78701 (email: jordan@everlywell.com).

multiple studies of lymphocyte activation gene 3 (*LAG-3*) therapy as a single agent or in combination are in progress; though only a few interim reports are currently available.[13]

HISTORY OF COMPANION DIAGNOSTICS

The idea of using biomarkers to predict response to cancer treatment has been actively pursued since the 1970s, when data were published showing improved tumor response to hormonal therapy in estrogen receptor–positive tumors compared with estrogen receptor–negative tumors.[14] In 1998, trastuzumab and its companion diagnostic, Dako's HercepTest, received FDA approval and marked the first instance of a drug being approved with an indication defined by the results of predictive biomarker testing.[15] This approval was followed several years later by the approval of cetuximab with a companion diagnostic test for *EGFR* status in patients with metastatic colorectal cancer.[16] This latter companion diagnostic's role as a predictive marker for cetuximab therapy was very quickly negated by improved understanding of colorectal cancer molecular pathology.[17] In 2014, the FDA formally issued guidance that defined a *companion diagnostic* as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." The labeling requirements in 2014 noted that for each companion diagnostic, a list of specific therapeutic products should be provided for which the companion diagnostic could be used. Per this guidance, the corresponding label for the therapeutic product, however, should specify the use of an FDA-approved companion diagnostic device, rather than a specific companion diagnostic product.[18] A related term, *complementary diagnostic*, first appeared in the 1990s when used by GlaxoSmithKline and Alizyme in reference to predictive genetic diagnostics.[19] In 2016, the FDA provided a preliminary definition for complementary diagnostics, defining them as "tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre-requisites for receiving the drug."[20] The key difference between complementary diagnostics and companion diagnostics is that for complementary diagnostics, the therapy has been shown to provide benefit regardless of the result, whereas for companion diagnostics, the result predicts safe or effective use of the therapeutic product.[15] For example, ICIs may benefit patients and PD-L1 immunohistochemistry (IHC) may be helpful in patient selection; however, PD-L1 positivity is not required to treat the patient with that particular therapy. Also, for many approved ICI treatment indications, no companion/complementary test is recommended. It was in this environment that the PD-L1 and PD-1 inhibitors first came to market. Of the PD-1 and PD-L1 inhibitors, pembrolizumab, nivolumab, and atezolizumab were each approved for indications requiring IHC companion diagnostic testing: PD-L1 IHC 22C3 pharmDx by Agilent/Dako, PD-L1 IHC 28-8 pharmDx by Agilent/Dako, and PD-L1 (SP142) IHC by Roche Tissue Diagnostics, for each ICI respectively. Durvalumab was approved with an available IHC complementary diagnostic testing PD-L1 IHC SP263 by Roche Diagnostics. Each of the IHC assays have different scoring systems for interpretation, and although none of these inhibitors have indications requiring the use of a specific companion diagnostic assay, confusingly, the indications for each inhibitor are founded on the scoring system for each IHC.[21–29] In 2018, the FDA revised its guidance regarding the labeling for companion diagnostics, allowing for companion diagnostic use for a class of therapeutics, rather than naming specific therapeutic products.[30] For the PD-L1 assays, relabeling the approved use of one of the assays to include the entire PD-1 and PD-L1 class of therapeutics would require that each scoring system be transferable to that assay, and attempts to demonstrate concordance among the assays developed in a clinical trial setting have shown generally acceptable results with some significant outliers.[31]

COMPLEXITY OF IMMUNE BIOLOGY AND THERAPEUTIC/DIAGNOSTIC REGULATORY LANDSCAPE

The immense complexity of the immune checkpoint system, combined with approvals of various drugs for differing, and overlapping, cancers linked to varying companion and/or complementary predictive screening tests (many with differing diagnostic endpoints) inevitably has led to significant levels of confusion for both surgical pathologists and medical oncologists. Though other technologies are being proposed to define subsets of patients likely to respond to ICIs (eg, tumor mutational burden,[32,33] gene expression,[34] multiplex IHC/immunofluorescence[35,36]), IHC-based detection of increased PD-L1 expression in the tumor/tumor microenvironment is the most commonly used predictive biomarker to identify patients likely to benefit from ICIs. IHC-based companion or complementary in vitro diagnostic (IVD) assays such as those for PD-L1 are validated for clinical use as multicomponent systems and viewed by regulatory agencies as fixed, integrated systems. Examples of these fixed components go beyond the primary antibody clone and include the antibody titer, the detection system including any amplification steps, the epitope retrieval method, the automated IHC staining instrument and software staining procedure, and the scoring system.[37] Any change to these component parameters would be considered by regulators as a deviation from the approved use of the assay that could potentially lead to staining differences and patient management impact. There are at least 12 different anti–PD-L1 directed antibody clones commercially available, with 6 having a significant commercial prominence. These are PD-L1 22C3, 28-8, and 73-10 (Agilent/Dako Technologies Inc); SP142 and SP263 (Roche Diagnostics); and E1L3N (Cell Signaling Technology).[38,39] Understanding the reproducibility between antibodies is of vital importance given the increasing need for pathology departments to integrate these assays into their workflows without having to validate multiple antibodies for differing clinical indications. Cross-comparisons between antibodies in differing cancer types have been performed to a limited degree given the immense number of potential combinations. The most common assessments have been in non–small cell lung cancer (NSCLC) and generally have shown good concordance of cancer expression, with significant exceptions, between antibodies.[40–44] For example, a meta-analysis of clinical trial and laboratory-developed assays comparing results between the 28-8, 22C3, SP142, and SP263 antibodies demonstrated high concordance, with the exception of SP142.[45] Multiple authors highlight that significant result differences between antibodies are likely secondary to laboratory protocol designs and their implementation rather than innate performance of the antibody/antigen interactions.[39,40,45,46] It is important to note that the

Table 1. US Food and Drug Administration–Approved Programmed Death Ligand-1 (PD-L1) In Vitro Diagnostic (IVD) Assays[a]

Assay/Antibody	Manufacturer	Detection System	Platform	Tissue Indications
PD-L1 IHC 22C3 pharmDx	Agilent/Dako	EnVision FLEX visualization system	Autostainer Link 48	Adenocarcinoma Cervical cancer ESCC GEJ HNSCC NSCLC TNBC UC
PD-L1 IHC 22C3 pharmDx	Agilent/Dako	EnVision FLEX visualization system	Dako Omnis	NSCLC
PD-L1 IHC 28-8 pharmDx	Agilent/Dako	EnVision FLEX visualization system	Autostainer Link 48	NSCLC SCCHN UC
Ventana PD-L1 (SP142) Assay	Roche Diagnostics	OptiView DAB IHC Detection Kit and OptiView Amplification Kit	BenchMark ULTRA	NSCLC TNBC
Ventana PD-L1 (SP263) Rabbit Monoclonal Primary Antibody	Roche Diagnostics	OptiView DAB IHC Detection Kit	BenchMark ULTRA	FFPE tissue (class I IVD)

Abbreviations: ESCC, esophageal squamous cell carcinoma; FFPE, formalin-fixed, paraffin-embedded; GEJ, gastric or gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; NSCLC, non–small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast carcinoma; UC, urothelial carcinoma.

[a] Source: manufacturer websites.

companion diagnostics for PD-L1 clones are paired with specific instrumentation for them to retain their companion diagnostic status. This has proven challenging for laboratories wanting to offer the various companion diagnostics for PD-L1. For example, if a laboratory wanted to offer PD-L1 companion diagnostics for the 3 approved drugs for NSCLC (Table 1), it would be required to purchase similar instrumentation from 2 manufacturers. This strategy is both expensive and inefficient. Laboratories do have the ability to validate the clones on nonapproved instrumentation; however, this test is then considered a laboratory-developed test (LDT) and loses its companion diagnostic status. Companion diagnostics are used to identify patients who will most likely benefit from therapy. A positive result is a prerequisite for therapy in these circumstances (Table 2). PD-L1 73-10 is under investigation as a companion diagnostic for the anti–PD-L1 avelumab.[43] PD-L1 SP263 and E1L3N antibodies have potential, along with others, as broad PD-L1 IHC assays.[46,47] Though the majority of patients treated with ICIs do not demonstrate an objective response, many studies demonstrate that tumor PD-L1 protein expression predicts a 3-fold increase in response compared with nonexpressers,[48–53] though even in this group responses can vary widely.[54–61] Importantly, a significant number of patients can show outcome improvement in spite of negative PD-L1 expression.[54,59] These real-world experiences readily imply that PD-L1 expression is only one of many factors that regulate ICI tumor responses and that further clarification of the role of PD-L1 IHC in patient stratification is clearly warranted. A noteworthy source of confusion relates to the PD-L1 scoring guidelines to identify patients likely to benefit from ICI therapy. There are 3 PD-L1 IHC scoring templates: the tumor proportion score (TPS), the combined positive score (CPS), and the tumor-infiltrating immune cells score. The TPS is the percentage of viable tumor cells showing partial or complete membrane staining. The CPS is the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Finally, the tumor-infiltrating immune cells score is the proportion of tumor area covered with any discernible PD-L1 staining of any intensity in immune cells. These metrics can vary with the cancers being treated by the same ICI assayed with the same antibody. For example, NSCLC patients assessed for treatment with pembrolizumab have their cancer assessed with 22C3 PD-L1 antibody, which is reported using the TPS system, with 1% or higher staining considered positive. However, the other 6 pembrolizumab approved indications requiring 22C3 PD-L1 IHC cancer screening are all reported using the CPS; 3 are called

Table 2. Approved Companion Diagnostics/Therapies[a]

Companion Diagnostic/Immune Checkpoint Inhibitor Combination	Cancers for Which Companion Diagnostic is Required for at Least a Subset of Cases[b]
PD-L1 22C3/pembrolizumab	NSCLC, gastric/gastroesophageal, cervical, urothelial, head and neck squamous cell carcinoma, triple-negative breast cancer
PD-L1 28-8/nivolumab and ipilimumab	NSCLC
PD-L1 SP142/atezolizumab	NSCLC, urothelial cancer, triple-negative breast cancer

Abbreviations: NSCLC, non–small cell lung cancer; PD-L1, programmed death ligand-1.

[a] Data derived from Theoret.[26]

[b] Companion diagnostics are not necessarily indicated for all clinical presentations of these cancers.

Table 3. Key Steps of Modified Root Cause Analysis			
	Title	Methodologies Used	Outcome
1	Timeline of the PD-L1 experience	Background presentations Open discussion	An agreed-upon timeline for companion diagnostic development and deployment based upon the PD-L1 experience
2	Create the ideal	Brainstorming session Discussion to review, understand and classify all suggestions	List of key principles of what an ideal companion diagnostic development and deployment could be
3	Identify the deviations	Open discussion to crosswalk the key principles identified in step 2 to the timeline created in step 1	List of deviations of the timeline in comparison with the ideal created in step 2
4	Corrective and preventative actions	Open discussion Priority matrices (specifically impact versus ease of accomplishment)	List of actions that can mitigate challenges with PD-L1 deployment and/or prevent challenges with future companion diagnostic development and deployment

Abbreviation: PD-L1, programmed death ligand-1.

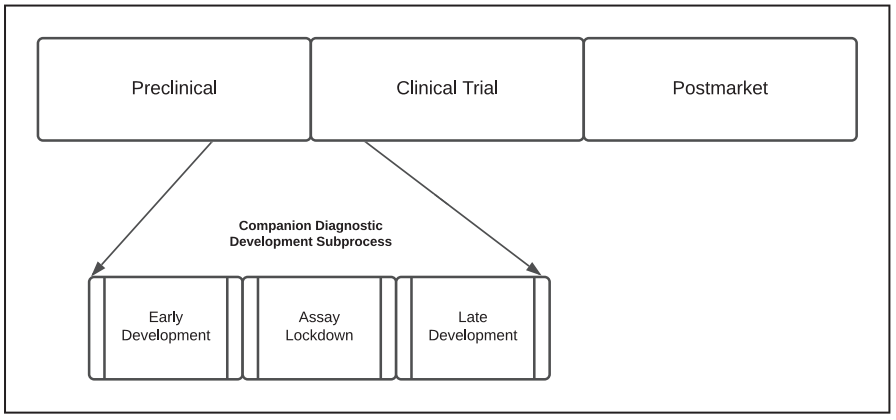
positive if CPS is 1 or higher and 3 are called positive if CPS is 10 or higher.[62] Percentage of positive staining of tumor-infiltrating immune cells has also been recently proposed as a complementary diagnostic assay for SP142 in conjunction with atezolizumab.[63] A number of studies[35,42,43] have demonstrated good interpathologist correlations in assessing PD-L1 membrane staining in tumor cells and applying prerequisite cutoffs and less accuracy when interpreting immune cell staining. A significant and still unresolved issue centers on tumor and tumor microenvironment spatial and temporal PD-L1 heterogeneity. Significant differences between PD-L1 expression within cancers,[64–66] between primary cancers and their metastases,[67] and before and after chemotherapy[68] have been noted in multiple cancer types. A uniform approach to deal with these problems has yet to emerge. These and other complexities related to PD-1/PD-L1 companion diagnostics are widely recognized as barriers to optimizing patient care. Importantly, without a better template for developing and implementing new companion diagnostics, especially for newer immunotherapies, the full potential of these therapies may not be realized.

PURPOSE

The purpose of this modified root cause analysis (mRCA) was to engage key stakeholder groups to review the events of the PD-L1 experience, identify opportunities to improve the current situation, and prevent future biomarker companion diagnostic challenges for novel and effective therapies. The expected outcomes of the mRCA included suggested solutions that are impactful, meaningful, and accomplishable. Further, they are intended to correct and prevent future challenges regarding companion diagnostic development and deployment into clinical practice.

METHODS

Prior to the mRCA meeting, key stakeholder categories were identified to include IVD companies and pharmaceutical companies, as well as the FDA. Within each of these categories, parties of interest were identified and invited to attend the October 11, 2019, PD-L1 in-person mRCA, hosted by the College of American Pathologists (CAP) Personalized Health Care Committee (PHC). Of import, all stakeholder categories were represented at the mRCA with the exception of the FDA, who had no representatives in attendance. This is a notable limitation of this report. A modified template for a traditional root cause analysis was used to structure the meeting.[69] The key discussion points in this framework were establishing the timeline of the PD-L1 experience, creating and describing an ideal process, identifying the currently accepted deviations from the proposed ideal process, and generating a set of corrective/preventative actions to avoid similar issues arising in the future. To elucidate a timeline of the PD-L1 experience and companion diagnostic development in general, background presentations were provided by leaders from within the pathology and pharmaceutical industries. These presentations discussed in detail how companion diagnostics are developed. Following the presentations, a moderated discussion ensued with input from all attendees. The discussion and insights enabled the group to agree upon a generic timeline for companion diagnostics development and deployment as well as the key characteristics of each of those stages. The next phase involved a formalized brainstorming session. Procedurally, attendees were challenged to rapidly and silently submit either concepts, processes, or characteristics of what an ideal companion diagnostic development and deployment should entail. Following a 5- to 10-minute brainstorming session, a moderated discussion reviewed and classified the submitted concepts. Key principles were identified and documented. These key principles for companion diagnostics development and deployment then served as landmarks for the next phase of the mRCA. With a timeline and ideal process documented, the third step in the mRCA was a moderated discussion to crosswalk the essential characteristics of the ideal process to the timeline described. This served as the primary step to identify the components of the PD-L1 timeline/experience that met or deviated from the determined ideal characteristics. The discussion challenged, refined, and enabled participants to understand the nuances of the key principles. The group then assessed whether each key principle was already present in a typical companion diagnostics development timeline. Conceptually, elements that meet these characteristics should be reinforced via the corrective and preventative assessment of the mRCA as well as alternative suggestions for the discordant elements from the ideal. The final step of the mRCA was to propose corrective and preventative actions. Corrective action refers to steps taken to help overcome some of the challenges of the PD-L1 experience thus far, and preventative action refers to steps taken to prevent similar challenges in future companion diagnostics development. Following the identification of potential corrective and preventative actions, each was placed within a priority matrix. This simple tool helps to visualize how to prioritize suggestions. The axes on this particular priority matrix were "ease of accomplishment" and "impact." This tool is a rapid way to help determine which actions are worthy of time and investment, and which may be too difficult to accomplish or have minimal impact. Priority matrices also help to ensure that the interventions follow the SMART principle[70]: specifically, to be impactful, actions should be specific, measurable, achievable, relevant, and time bound. Numerous suggestions were discussed and narrowed down to a select few via the use of priority matrices. The key steps of the mRCA, including methodology and expected outcomes, are summarized in Table 3.



Major drug development phases: The "typical lifecycle" of a companion diagnostic. Note: This largely represents the timeline of how programmed death ligand-1 immunohistochemistry was developed and implemented. Other companion diagnostics, depending upon how they follow "the science" may have different critical paths.

RESULTS

Timeline of the PD-L1 Experience

The discussion focused on the typical process for developing a companion diagnostic and the critical time points throughout. Key questions to be answered were: At what point in the drug development pathway is the need for a companion diagnostic realized? Is the time point when a companion diagnostic is needed consistent or standardized from drug to drug or company to company? Once the need is recognized, what are the processes to develop and lock down the assay? At what point in the process is the companion diagnostic revealed to the clinical community? Is there a general process in which the clinical community can comment on the companion diagnostic to ensure appropriate clinical adoption? And finally, what is the regulatory process that surrounds companion diagnostic development? Is it consistent from drug to drug or company to company? The findings showed that the need for a companion diagnostic follows the science. This means that as more about the drug, its interaction with various biomarkers, and the stratification of effectiveness in relation to those biomarkers is understood, the need for a companion diagnostic becomes apparent. In other words, when following the science at any time point in the drug development process, it is possible to realize the need for a companion diagnostic. Accordingly, there is no standard entry point for the need of a companion diagnostic. Often, the diagnostic precedes drug development (eg, breast cancer gene [*BRCA*] testing and poly [ADP-ribose] polymerase [*PARP*] inhibitors), or the companion diagnostic is codeveloped with the drug (eg, PD-L1 IHC and various immunotherapies), and finally, the companion diagnostic could be developed after the drug (eg, fluorescence in situ hybridization and neurotrophic tyrosine receptor kinase [*NTRK*] inhibitors). The specific answers to these fundamental questions highlight the variability and lack of standardization throughout the drug development process. The group understood that these multiple pathways of companion diagnostics development are inherent in the complexities of discovery and implementation of new therapies, yet recognized the difficulty it causes to improve clinical adoption of these tests. Once the need is recognized, what are the processes to develop and lock down the assay? What is the regulatory process that surrounds companion diagnostics? The group reviewed the process of FDA regulation of companion diagnostics, which in general requires manufacturers to submit both analytical and clinical validity data to support the test and the claims it makes. These assays are generally created with the current knowledge in the medical literature, as well as proprietary knowledge within the pharmaceutical company. Once the FDA has given its approval for the diagnostic, the assays are locked down. *Locked down* refers to the entire analytical process, including specimen type, reagents, instrumentation, interpretation, etc, and is deemed immutable to maintain FDA approval and to uphold the claims for the companion diagnostic. Any modification of an FDA-approved diagnostic assay then defaults to the regulation of LDTs. This is an important distinction; as the science and knowledge progress in relation to the biomarker/drug association, companion diagnostics are infrequently updated, and thus commonly fall behind the expanding knowledge base of the medical community. At what point in the process is the companion diagnostic revealed to the clinical community? Is there a general process in which the clinical community can comment on the companion diagnostic to ensure appropriate clinical adoption? As much of the drug development process is proprietary, the disclosure to the clinical community typically occurs quite late in the drug development process, particularly with regard to the companion diagnostic. This is because generally large clinical trials must at least be underway, if not completed, to fully elucidate the clinical value of a biomarker–companion diagnostics relationship. In general, the reveal occurs near or following the completion of the clinical trial (Figure). These results are often presented at clinical conferences such as the major oncology conferences in the United States and the European Union. Interestingly, it was felt that disclosure to the oncology community typically predated disclosure to the pathology community. Pairing the typical milestones in drug/diagnostic development and the late reveal of the drug/diagnostic clinical impact of the clinical trial; the pathology community has little to no opportunity to comment on the appropriateness of the companion diagnostic, the ease of its clinical deployment into clinical laboratories, and thus patient access to the diagnostic and the subsequent pharmaceutical.

Create the Ideal/Identify Deviations

The group discussed what a potential ideal strategy for companion diagnostics implementation would require. A critically important attribute of this process was to conceive of a blueprint unencumbered by preconceptions of current companion diagnostics development processes. Developing this ideal doesn't necessarily indicate the medical commu-

nity should rebuild the existing structure for companion diagnostics, as we all believe that is not plausible; however, the process of creating an ideal companion diagnostic development pathway assisted in identifying key principles to successful development process. The outcome of this session was the generation of the following key principles to help guide all stakeholders in potentially shifting the existing pathway to one that is more streamlined, transparent, and effective. Specifically, these key principles include communication, flexibility, collaboration, quality, and finance.

Communication.—Communication is a critical component to any successful process and should encompass all key stakeholders. As a reminder, the key stakeholders in the companion diagnostic development space include pharmaceutical companies, IVD manufacturers, regulators (ie, FDA and Centers for Medicare & Medicaid Services), and, equally as important, the end users of the drug-diagnostic pairing, the treating clinician and pathologist. As learned from the earlier step in this study, of building the companion diagnostic timeline, the latter key stakeholders are generally engaged late in the development process, typically after preliminary clinical trial results are made public and after the companion diagnostic assay is locked down. With the PD-L1 experience, it was discussed that the oncology field was engaged early in the concept development via abstracts and presentations at professional society annual meetings. Only afterward were the pathology organizations more deeply informed, often after PD-L1 IHC deployment challenges were already faced by numerous laboratories. Accordingly, the group felt it was critically important that the current process be reviewed to encourage earlier and meaningful communication to these late yet crucial stakeholders to guide companion diagnostic development, and, more importantly, to ensure smooth clinical deployment of such assays in the innumerable clinical laboratories across the United States and the world.

Flexibility.—The group discussed the central role of the FDA in approving companion diagnostics. Following review by the FDA, a diagnostic may obtain FDA approval based upon the specific claims of the diagnostic's intended use. Of note, the intended use statements are carefully written to provide a claim for the diagnostic based solely on the data submitted with the filing. They do not include all information that may exist in the medical literature, etc. Frequently, once a diagnostic has received FDA approval, even as the medical literature and knowledge base continues to expand, typically no additional data are submitted to the FDA to update the intended use claims. Once a laboratory uses an FDA-approved assay outside of the intended use claims, the test defaults to a high-complexity LDT. Examples of such expansion of clinical utility beyond the intended use claim of companion diagnostics includes FDA-approved assays for B-Raf proto-oncogene (*BRAF*) V600E mutations in melanoma and erb-b2 receptor tyrosine kinase 2 (*ERBB2*) amplification in breast cancer. Both assays are now frequently used in other clinical scenarios, such as *BRAF* mutations in nonmelanocytic tumors (eg, lung cancer), or even within melanoma, with the recognition that other non-V600E mutations are sensitive to the specific inhibitors. Similarly, human epidermal growth factor receptor 2 (HER2) protein overexpression and/or gene amplification is commonly used in gastric carcinoma as an off-label indication despite its clinical utility being well documented in the medical literature. The general inflexibility of the regulatory review process and the infrequency of manufacturers' attempts to expand the clinical claims for the assay lead to significant confusion for diagnosing pathology departments and treating clinicians. The group felt that to prevent future challenges akin to the PD-L1 clinical deployment, the regulatory environment and process of companion diagnostics requires reform to have built-in flexibility to update the intended use claims as the medical literature and knowledge base continue to expand.

Collaboration.—Interdisciplinary and interprofessional collaboration was felt to represent a great opportunity to improve the clinical deployment of companion diagnostics. Upon reviewing the typical process of companion diagnostic development, it became apparent that information is shared in a stepwise fashion. Much of the development begins within the pharmaceutical company, with possible engagement with an IVD manufacturer, and is typically followed by communication to oncology and finally pathology communities. This stepwise path of communication typically occurs too late to allow the clinical professional societies to provide feedback on how easily a particular companion diagnostic could be deployed in the real world. The group felt, at least in part, that this late communication contributed to the challenging deployment of PD-L1 biomarker testing via IHC. Looking to the future, earlier and meaningful disclosure to the clinical and pathology communities regarding biomarker and companion diagnostic development would result in real-life feedback to ensure the companion diagnostic could fit into real-world medical workflows.

Quality.—Discussions included quality management of companion diagnostic development as well as of the clinical trials that support the biomarker-therapeutic relationship. In addition to the premarket quality program to ensure an effective diagnostic, the group discussed features of an effective postmarket quality management program. Recognizing that the FDA already has a postmarket program for quality that monitors adverse patient outcomes based upon the therapeutic or the companion diagnostic, the group felt that pharmaceutical companies also have a critical role in the quality of the successful deployment of a companion diagnostic. In this exercise of creating the ideal, it was felt that key attributes of an effective deployment should include robust postmarket quality assurance measures, including but not limited to laboratory training programs and ongoing assessment of quality. Specifically, initial laboratory training programs should ensure that technologists and pathologists are aware of how to perform and interpret the diagnostic, respectively. Key attributes of the training programs should include emphasis on indications for using the drug/companion diagnostics to ensure the correct scoring system is performed and performed correctly. Ongoing assessment should include defined intervals of challenges to the laboratories performing these diagnostics, akin to proficiency testing. In addition, as many of the clinical indications of these drugs and companion diagnostics change and/or are added to over time, pharmaceutical companies should develop robust communication programs to keep clinical laboratories and clinicians up to date and provide ongoing support to navigate the changing landscape.

Financial.—In the companion diagnostic space, there are a multitude of stakeholders, including the pharmaceutical industry, IVD manufacturers, regulatory agencies, clinical providers, and laboratory professionals, as well as patients.

Although all perspectives are important, specifically understanding the financial incentives of each stakeholder is vital to devise a companion diagnostic development process that meets all stakeholders' needs. It is critically important to appreciate the impact financial misalignment has on companion diagnostic deployment. Referring to some of the other components of the ideal, balancing the financial perspective with collaboration and communication could be a delicate act. For example, early communication/collaboration between the pharmaceutical industry and laboratory professionals about assay design, etc, could result in a premature release of intellectual property that threatens the financial goals of the pharmaceutical company. Early communication/collaboration also places risk for intellectual property or market share concerns for those companies that will ultimately manufacture the companion diagnostic. The current environment, which is designed to protect intellectual property, is a contributing factor that delays communication to the downstream stakeholders, such as clinical providers, laboratory professionals, and patients. Without reevaluation and realignment of the financial incentives across all key stakeholders, future deployments of companion diagnostics may suffer the same clinical challenges that PD-L1 biomarkers/companion diagnostics have faced. The authors recognize that financial misalignment is very challenging to address in the future without a significant overhaul of the industry. Our suggested corrective/preventative action could be considered a first step in driving the necessary change for more successful deployments in the future.

Suggested Corrective/Preventative Actions

Output of the mRCA was designed to include suggested corrective and preventative actions regarding the PD-L1 experience, as well as future companion diagnostic deployment. The specific recommendations are below.

Pharma Advisory Board.—This entity would address the need for improved collaboration during the preclinical trial phase by providing a safe, impartial environment that can facilitate collaboration among stakeholders while protecting the financial interests of all parties. The primary goal of this advisory board is to provide a platform for pharmaceutical, IVD, medical oncology, and pathology industry representatives to speak freely under confidence about companion diagnostic development. Furthermore, the board could serve to vet upcoming companion diagnostics for feasibility and harmonization/standardization. The most practical way of implementing this would be to engage an already existing, impartial entity in industry, such as TransCelerate Biopharma, an organization with the mission statement of promoting and fostering collaboration among pharmaceutical companies for improved efficiencies and impact.

FDA Advocacy.—Achieving regulatory flexibility regarding companion diagnostic assay changes during and after the lockdown phase may not happen quickly. However, these changes would serve all stakeholders well and thus justify the development of an advocacy plan to engage the FDA by (1) expressing the challenges of assay lockdown with respect to the impact it has on patient care and (2) exploring/suggesting pathways to allow more flexibility in companion diagnostic development, such as by leveraging the FDA's "Adaptive Design Clinical Trials" guidance.[71]

CAP Distribution of Cross-Disciplinary Information.—As a means to improve cross-disciplinary communication in the clinical trial phase of development, the CAP provides an excellent potential avenue for accessing members of both the IVD industry and the pathology community. One approach the CAP could use to improve communication is the development of more robust avenues to attain and distribute cross-disciplinary information to all or selected subsets of CAP membership. Provided that this mRCA is focused on companion diagnostics, and that companion diagnostics are commonplace in the oncology space, oncology would be an ideal pilot program.

Membership Alliance.—A second approach to improving cross-disciplinary communication during the clinical trial phase is by facilitating and encouraging cross-disciplinary society membership. The CAP and other cross-disciplinary professional societies (eg, American Society of Clinical Oncology) could develop an alliance to provide lower-cost, midlevel membership to their respective members. This would promote cross-disciplinary communication and collaboration, and it would provide the pathology community with additional avenues of information from other disciplines that have significant impact on pathology services. Such an alliance would also provide the equivalent benefit of oncologists gaining insight into pathology-related issues that impact their services.

Biomarker Training.—Frequently, if not universally, pharmaceutical companies create training programs for companion diagnostics. The quality deficiencies encountered in postmarket PD-L1 companion diagnostic training demonstrate a need for improved organization and oversight of this training. The CAP could fill this need by becoming a clearinghouse for such training opportunities (requirements), which could even be converted into continuing medical education opportunities.

DISCUSSION

The mRCA performed on the PD-L1 experience was an effective method to engage key stakeholders and discuss the challenges faced with PD-L1. Overall, there is significant, if not universal, agreement that the PD-L1 experience has led to significant challenges for all parties involved, up to and including patients. The representatives of the PHC and the diagnostics and pharmaceutical industries who were present endorsed these findings and feel there would be interindustry support to implement these corrective and preventative actions to reduce the potential negative impact of future companion diagnostic implementations. Although most key stakeholders were present, a limitation of this manuscript is the absence of representation of the FDA. Recognizing that the FDA is a critical stakeholder in companion diagnostic requirements, the CAP PHC and the Council on Government and Professional Affairs are engaging with the FDA through other methods to obtain input. Also, because of issues related to timing, representatives from clinical oncology and patient representatives were not present. The spirit of companion diagnostics is honorable and is designed to ensure the correct results are obtained and incorporated into clinical management decision to provide the right drug for the right patient at the right time. In the current environment of regulation, competition, and continuous knowledge growth the committee recognized several concrete steps are possible to improve the likelihood of smoother implementation of new companion diagnostics and related treatments to patients. Although we hope that these corrective actions have a positive impact on future companion diagnostics, we largely

focused on actionable and impactful interventions that were within the realm of influence of the CAP. It is important to stress that there are alternative, and potentially more impactful, corrective actions that can be undertaken to improve the experience of future companion diagnostics. We hope that the stakeholders, both those directly involved in this project and those reading this manuscript, identify what actions they can initiate to improve the clinically successful deployment of companion diagnostics to come.

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