

TUTORIAL

Current Status of Companion and Complementary Diagnostics

Strategic Considerations for Development and Launch

H Scheerens¹, A Malong¹, K Bassett¹, Z Boyd¹, V Gupta¹, J Harris¹, C Mesick¹, S Simnett¹, H Stevens², H Gilbert¹, P Risser¹, R Kalamegham¹, J Jordan², J Engel², S Chen², L Essioux³ and JA Williams¹

US Food and Drug Administration (FDA)-approved diagnostic assays play an increasingly common role in managing patients to prolong lifespan while also enhancing quality of life. Diagnostic assays can be essential for the safe and effective use of therapeutics (*companion diagnostic*), or may inform on improving the benefit/risk ratio without restricting drug access (*complementary diagnostic*). This tutorial reviews strategic considerations for drug and assay development resulting in FDA-approved companion or complementary diagnostic status.

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INTRODUCTION

Scope and definition of concepts

The key scope of this article focuses on companion and complementary diagnostic status as determined by the FDA. However, there are also specific references to testing status in the European Union (EU) and other geographic regions. The following concepts are defined briefly below and in the Glossary of Terms (**Table 1**): *Analytical validation*: establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is *validation* of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness; *Clinical validation*: establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest; *Clinical utility*: the conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.¹

OVERVIEW

Several considerations are relevant for optimizing personalized healthcare (PHC) and improving access to new therapies for patients via positive clinical studies and subsequent regulatory approvals. The term PHC refers to developing targeted therapeutics for specific patients or patient subgroups (i.e., genotypes/phenotypes/endotypes) or optimizing dosing for certain patient subgroups.^{2,3} The objective of PHC

is to identify and help direct therapies to patients who are most likely to experience a favorable benefit–risk outcome with a selected therapy. This is best accomplished by identifying patients who are most likely to experience enhanced benefits and/or decreased risks associated with a therapy, and if not, also restricting access of the therapy to patients who are most likely to experience a positive benefit–risk profile with the therapy. For example, it has been shown that the subgroup of women with breast cancer who overexpress the human epidermal growth factor receptor 2 (HER2) protein derive clinically meaningful responses to trastuzumab (HERCEPTIN), an anti-HER2 monoclonal antibody.⁴ This led to the development of companion diagnostic assays for HER2 where a positive result confirming overexpression is required for patients to receive trastuzumab (HERCEPTIN), and other HER2-directed therapies such as pertuzumab (PERJETA) and ado-trastuzumab emtansine (KADCYLA).

Significant advances are being made in understanding the complex biologies of disease, including those influenced by immune mechanisms such as cancer⁵ and asthma, which comprises specific clinical phenotypes and underlying molecular endotypes.^{3,6} Most approved drugs for these diseases have limitations in that they are either only partly effective in all patients, also known as an all-comer population, show increased benefits in a subset of patients, and/or that patients generally respond less robustly over time. These observations are strongly suggestive of multiple molecular pathways driving the underlying pathophysiology in these different subgroups of patients, or possibly of resistance mechanisms emerging to overcome drug efficacy, or both. The obvious implication of this is that different patients may need different therapeutics to treat their disease, but how does one know which patient needs which treatment?

¹Genentech Inc., San Francisco, California, USA; ²Roche AG, Basel, Switzerland; ³Pharmaceutical Sciences, Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche, Ltd, Basel, Switzerland. Correspondence: JA Williams (Williams.james@gene.com)
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Table 1 Glossary of Terms

Term	Definition*
Analytical validation (1)	Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test's, tool's, or instrument's technical performance, but is not validation of the item's usefulness.
Clinical validation (1)	Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest;
Clinical utility (1)	The conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations.
Companion Diagnostic	A companion diagnostic is a medical device, often an <i>in vitro</i> device (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product.
Complementary Diagnostic** (Draft definition from FDA as presented at ASCO – 5 June 2016)	A complementary diagnostic is a test that aids in the benefit–risk decision–making about the use of the therapeutic product, where the difference in benefit–risk is clinically meaningful. Complementary IVD information is included in the therapeutic product labeling.
Enrichment	Enrichment is the prospective use of any patient characteristic, including demographic, pathophysiologic, historical, genetic, and others, to select patients for a study or to analyze patient data to obtain a study population in which detection of a drug effect is more likely than it would be in an unenriched population.
<i>In Vitro</i> Diagnostic (IVD)	IVD products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.
Premarket Approval (PMA)	Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, the FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices. Therefore, these devices require a PMA application (submission via modules is an option) under section 515 of the Food, Drug and Cosmetic Act to obtain marketing clearance.

*Source: FDA.

**As of December 2016, no formal FDA definition exists for complementary diagnostics. ASCO, American Society of Clinical Oncology.

As defined by BEST,¹ predictive biomarkers are biomarkers used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent. So, predictive biomarkers can be used to identify patient subgroups that best benefit from targeted therapies. Targeting those biomarker-defined subgroups with novel therapeutics could result in enhanced efficacy compared with all-comer populations and reduce unnecessary exposure to subgroups not deriving optimal benefit. Prognostic biomarkers are defined as biomarkers used to identify likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest.¹ Predictive biomarkers of treatment response could at the same time also be prognostic for clinical events or disease progression. However, in the context of identifying patient subgroups with enhanced response and associated companion or complementary diagnostic development, these biomarkers are referred to as predictive for treatment response. Subsequent analytical and clinical validation of assays for these biomarkers can lead to the marketing approval of companion diagnostics or, more recently, complementary diagnostics via FDA approval in the United States. Examples of analytical platforms for diagnostic assays are immunohistochemistry (IHC) and quantitative polymerase chain reaction (qPCR), and these are likely to increase as the field evolves to include platforms such as next-generation sequencing (NGS),⁷ imaging, and possibly immunoassays.

Although two *complementary* diagnostics for programmed death-ligand 1 (PD-L1) IHC assays for cancer immune thera-

pies (as described in detail in later sections) have received FDA approval, formal guidance describing the term and providing a framework for approval is pending. In contrast to companion diagnostics, complementary diagnostics do not restrict patients from receiving codeveloped therapies based on the outcome of the diagnostic test. This is because therapeutic benefit has been demonstrated in all patients for complementary diagnostics, regardless of biomarker status. Nevertheless, the biomarker can inform on enhanced benefits in subgroups of patients; for example, those expressing higher protein levels of the immune checkpoint PD-L1. These early PD-L1 IHC assay precedents of complementary diagnostics are currently limited to cancer immune therapies, namely, atezolizumab (TECENTRIQ for bladder and non-small cell lung cancer (NSCLC) indications) and nivolumab (OPDIVO for melanoma and NSCLC indications). However, it is likely that they will be joined by other assays with complementary diagnostic status more broadly across therapeutic areas that will include additional examples in oncology as drug combinations become more commonly used.

Historical context and case studies

Figure 1 shows a timeline of key events for development of diagnostic assays partnered to therapeutics in the United States. The FDA approved the first companion diagnostic (HER2 assay for trastuzumab) in 1998,⁸ and the first complementary diagnostic (PD-L1 IHC assay for nivolumab) in 2015. Although the term “complementary diagnostic” has been used since the 1990s, the FDA regulatory status did not apply until 2015. Prior to 2015, the term “complementary diagnostic” referred to tests used to improve disease

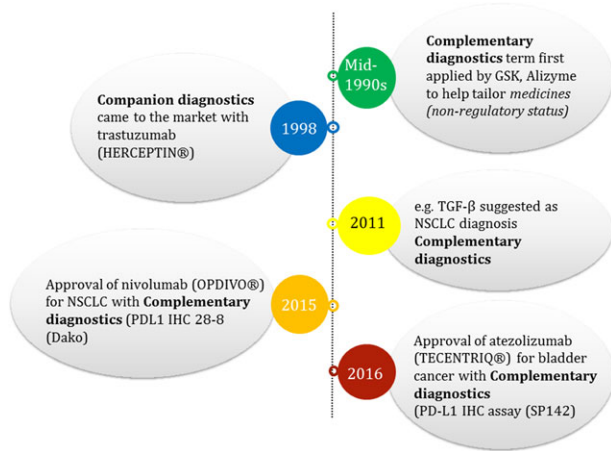


Figure 1 Historical timeline of the first Companion and first Complementary Diagnostic assays in the United States.

management, early diagnosis, patient risk stratification, and drug monitoring, but did not require a regulatory link to a specific therapeutic.⁹

Trastuzumab (HERCEPTIN) has been shown to improve overall survival in both adjuvant and metastatic HER2-positive (HER2 protein overexpression in tumor tissue) breast cancer in patients.⁴ Thus, the HER2 test became the first companion diagnostic (**Figure 1**). Additional assays to measure HER2 have since been approved and now make up nearly half of all companion diagnostics approved by the FDA (**Table 2**). Importantly, most of these HER2 assays were not codeveloped with trastuzumab, but were instead approved after the initial drug approval as technologies and commercial opportunities evolved. The focus of the current tutorial is on strategic codevelopment of the drug and assay.

An excellent example of a companion diagnostic approval is the COBAS BRAF V600E test which received simultaneous FDA marketing approval along with vemurafenib (ZELBORAF) for metastatic melanoma. Data showed an overall survival benefit for patients with the BRAF V600E mutation relative to the comparator treatment, dacarbazine.¹⁰ Additionally, studies showed paradoxical activation of the RAF pathway in cell lines with wildtype status suggests potential harm to patients without the V600E mutation receiving this therapy, as reflected in the product label. Clearly, V600E mutation status is essential for the safe and effective use of vemurafenib (ZELBORAF) in metastatic melanoma. Recognizing this fact, the sponsors undertook a regulatory strategy that included parallel development of the drug and its associated assay. The simultaneous approval of the two represents an important example of a codeveloped drug and diagnostic assay.

The first two approvals for complementary diagnostic assays highlight the FDA's determination that patients should not be excluded from receiving cancer immune therapies even though efficacy in response to therapy increased with higher levels of PD-L1 protein expression levels in their tumors. Importantly, although the FDA drug approvals promote access for all patients to receive therapy, both PD-L1

IHC assays identify patients who may respond better to these drugs as the levels of PD-L1 protein expressed in tumors increase. In 2015 the FDA approved the first complementary diagnostic using the PD-L1 IHC 28-8 PharmDx assay (<http://www.agilent.com/en-us/products/pharmdx/pd-l1-ihc-28-8-pharmdx/pd-l1-ihc-28-8-pharmdx-for-autostainer-link-48-1>) for the cancer immunotherapy nivolumab (OPDIVO) based on a phase III trial in second-line non-small cell lung cancer (NSCLC).¹¹ Separately, positive PD-L1 status as determined by PD-L1 IHC 28-8 PharmDx in melanoma is correlated with the magnitude of the treatment effect on progression-free survival (PFS) from nivolumab (OPDIVO). PD-L1 protein expression is defined as the percentage of tumor cells exhibiting positive membrane staining at any intensity, which may be associated with enhanced survival from nivolumab (OPDIVO) in nonsquamous NSCLC. In 2016 the FDA approved complementary diagnostic status for the VENTANA PD-L1 (SP142) assay based on successful pivotal trials with atezolizumab (TECENTRIQ) in NSCLC¹² and bladder cancer.⁵ The SP142 IHC assay is a qualitative immunohistochemical assay intended for use in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma and NSCLC tissue (<http://www.ventana.com/product/1827?type=2357>). Scoring and interpretation of PD-L1 status is indication-specific. Discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering $\geq 5\%$ of tumor area determined by the VENTANA PD-L1 (SP142) assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a nonrandomized study of atezolizumab (TECENTRIQ). In NSCLC, discernible PD-L1 membrane staining of any intensity in $\geq 50\%$ of tumor cells or tumor infiltrating immune cells covering $\geq 10\%$ of tumor area occupied by tumor cells as determined by the VENTANA PD-L1 (SP142) assay may be associated with enhanced overall survival (OS) from atezolizumab (TECENTRIQ).

What is different outside the United States?

In the United States, the FDA regulates the approval of companion and complementary *in vitro* diagnostic (IVD) tests via the Center for Devices and Radiological Health (CDRH). The package insert (product label) of a therapeutic usually states "as determined by an FDA-approved test," when referring to the biomarker assays used to identify a subgroup of patients. FDA approval ensures verification of both analytical and clinical validation of the IVD test. The package insert of the diagnostic assay will refer back to the therapeutic with which the test is intended to be used. In Europe, the summary of product characteristics (SmPC) describes the therapeutic and refers to the diagnostic assay "as determined by an accurate and validated assay." The European Medicines Agency's Committee on Medical Products for Human Use (EMA CHMP) does not regulate or approve the diagnostic test; rather, marketing of test requires that the sponsor obtain a "CE" marking. CE marking (Conformité Européene) indicates that the product had been assessed and meets European Union (EU) safety, health, and environmental protection requirements (<http://ec.europa.eu/growth/single-market/ce-marking/>). For example, the herceptin SmPC states "HER2 testing must be performed in a specialized laboratory which can ensure adequate validation of the testing procedures"

Table 2 List of all approved companion and complementary diagnostic assays in the United States

Companion Diagnostic Assays (listed in alphabetic order of drug trade name)				
Drug trade name (generic name)	Device trade name	Disease	Platform	
1	ERBITUX (cetuximab); VECTIBIX (panitumumab)	DAKO EGFR PharmDx Kit	Colorectal cancer	● IHC
2	ERBITUX (cetuximab); VECTIBIX (panitumumab)	The cobas KRAS Mutation Test	Colorectal cancer	● PCR
3	ERBITUX (cetuximab); VECTIBIX (panitumumab)	<i>therascreen</i> KRAS RGQ PCR Kit	Colorectal cancer	● PCR
4	EXJADE (deferasirox)	Ferriscan	Thalassemia	● MRI
5	GILOTRIF (afatinib)	<i>therascreen</i> EGFR RGQ PCR Kit	Non-small cell lung cancer	● PCR
6	GLEEVEC (imatinib mesylate)	DAKO C-KIT PharmDx	Gastrointestinal stromal tumor	● IHC
7	GLEEVEC (imatinib mesylate)	<i>PDGFRB</i> FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)	Myelodysplastic Syndrome/Myeloproliferative Disease	● FISH
8	GLEEVEC (imatinib mesylate)	<i>KIT</i> D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM)	Aggressive systemic mastocytosis	● PCR
9	HERCEPTIN (trastuzumab)	INFORM HER-2/NEU	Breast cancer	● FISH
10	HERCEPTIN (trastuzumab)	INSITE HER-2/NEU KIT	Breast cancer	● IHC
11	HERCEPTIN (trastuzumab)	Bond Oracle Her2 IHC System	Breast cancer	● IHC
12	HERCEPTIN (trastuzumab)	PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody	Breast cancer	● IHC
13	HERCEPTIN (trastuzumab)	SPOT-LIGHT HER2 CISH Kit	Breast cancer	● CISH
14	HERCEPTIN (trastuzumab)	PATHVYSION HER-2 DNA Probe Kit	Breast cancer	● FISH
15	HERCEPTIN (trastuzumab)	INFORM HER2 DUAL ISH DNA Probe Cocktail	Breast cancer	● ISH
16	HERCEPTIN (trastuzumab)	Bond Oracle Her2 IHC System	Breast cancer	● IHC
17	HERCEPTIN (trastuzumab); PERJETA (pertuzumab); KADCYLA (ado-trastuzumab emtansine)	HERCEPTEST	Breast cancer	● IHC
18	HERCEPTIN (trastuzumab); PERJETA (pertuzumab); KADCYLA (ado-trastuzumab emtansine)	HER2 FISH PharmDx Kit	Breast cancer	● FISH
19	IRESSA(gefitinib)	<i>therascreen</i> EGFR RGQ PCR Kit	Non-small cell lung cancer	● PCR
20	KEYTRUDA (pembrolizumab)	PD-L1 IHC 22C3 PharmDx	Non-small cell lung cancer	● IHC
21	LYNPARZA (olaparib)	BRACAnalysis CDx	Ovarian cancer	● PCR
22	MEKINIST (trametinib); TAFINLAR(dabrafenib)	THxID BRAF Kit	Melanoma	● PCR
23	RUBRACA (rucaparib)	FoundationFocus CDxBRCA Test	Ovarian cancer	● NGS
24	TAGRISSO (osimertinib)	cobas EGFR Mutation Test v2	Non-small cell lung cancer	● PCR ● PCR
25	TARCEVA (erlotinib)	cobas EGFR Mutation Test	Non-small cell lung cancer	● PCR

(Continued)

Table 2 Continued

Companion Diagnostic Assays (listed in alphabetic order of drug trade name)				
Drug trade name (generic name)	Device trade name	Disease	Platform	
26	VENCLEXTA (venetoclax)	VYSIS CLL FISH Probe Kit	Chronic lymphocytic leukemia	● FISH
27	XALKORI (crizotinib)	VENTANA ALK (D5F3) CDx Assay	Non-small cell lung cancer	● IHC
28	XALKORI (crizotinib)	VYSIS ALK Break Apart FISH Probe Kit	Non-small cell lung cancer	● FISH
29	XALKORI (crizotinib)	VENTANA ALK (D5F3) CDx Assay	Non-small cell lung cancer	● IHC
30	ZELBORAF (vemurafenib)	COBAS 4800 BRAF V600 Mutation Test	Melanoma	● PCR
Complementary Diagnostic Assays (listed in alphabetic order of drug trade name)				
Drug trade name (generic name)	Device trade name	Disease	Assay format	
1	OPDIVO (nivolumab)	PD-L1 IHC 28-8	Melanoma Non-small cell lung cancer	● IHC
2	TECENTRIQ (atezolizumab)	VENTANA PD-L1 (SP142) Assay	Bladder cancer Non-small cell lung cancer	● IHC

IHC, Immunohistochemistry; PCR, Real-time polymerase chain reaction; MRI, Magnetic resonance imaging; FISH, Fluorescence *in situ* hybridization; ISH, *In situ* hybridization; CISH, Chromogenic *in situ* hybridization; NGS, Next-generation sequencing.

and “for any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.”

In the EU specifically, regulation of medical devices has been separated from the regulation of pharmaceuticals. However, there is growing momentum towards release of new guidance documents that may integrate the two paths (diagnostic and therapeutic) as more are codeveloped and as the diagnostic assays increasingly become more technologically sophisticated.¹³ In the meantime, CE-marking for *analytical* grade tests without associated clinical outcome data can precede tests with *predictive* status when associated clinical data are available. Therefore, an analytical assay can be marketed with limited information about clinical utility before it is marketed to inform on predicted response to a treatment. The nivolumab (OPDIVO) 28-8 and atezolizumab PD-L1 (TECENTRIQ) IHC tests are two examples, where each assay has shown increasing efficacy with increasing levels of PD-L1 expression. Additionally, analytical concordance studies can enable cross-referencing of CE marking between assays for the same therapy, such as for the Ventana SP263 PD-L1 IHC assay (<http://www.ventana.com/ventana-pd-l1-sp263-assay-2/>) to nivolumab (OPDIVO) following a concordance study with the 28-8 IHC assay.

In addition to the difference in regulatory status of the diagnostic test (FDA-approved vs. CE marking), the payer environment outside the United States is also vastly different. As explained in the section on reimbursement and commercial considerations, certain geographic regions may only reimburse for subgroups of patients with enhanced clinical benefit, even in the case of an all-comer label with a complemen-

tary diagnostic where no patients are restricted from receiving the drug.

Considerations for nononcology indications

The vast majority of companion diagnostics and all complementary diagnostics are currently in oncological indications, perhaps because of the plethora of targeted therapies developed in this indication reflecting our increasingly sophisticated understanding of the genetic and immunologic pathways underlying various cancers. The diagnostic assay typically measures expression of the therapeutic target in the tumor tissue or mutations in the gene of the therapeutic target (Table 2), clearly linking the biomarker measured by the diagnostic test to the mechanism of action of the therapeutic. In nononcological indications, this is often either not clinically feasible, or with current technologies, impossible. For example, in many neurologic, respiratory, ophthalmologic, or rheumatologic diseases, obtaining diseased tissue for routine sampling is often not easy, making it difficult to measure target levels in the relevant organ in current clinical practice and leading to a greater reliance on distal blood-based biomarkers. No common somatic or germline genetic variations were identified so far as major factors driving disease pathology in these diseases. For these reasons, identifying a subgroup of patients most likely to respond to a therapeutic by measuring the target in a biopsy specimen from the diseased tissue is often less feasible than in other (but not all) oncologic diseases where tissue is routinely biopsied.

One approach that has been used to identify molecular endotypes within a disease is through observational experimental medicine studies whereby disease tissue samples are profiled molecularly. For example, Woodruff *et al.* first described TH2-high and TH2-low subgroups of asthma patients based on gene expression of bronchial epithelial brushings.¹⁴ Subsequently, bronchial epithelial gene

expression was correlated with biomarkers that were easily detected in peripheral blood, and based on this analysis serum periostin was selected as a candidate diagnostic used to identify asthma patients with TH2-driven disease.¹⁵ McKinney *et al.* eloquently demonstrated disease heterogeneity based on peripheral blood T-cell exhaustion phenotype in autoimmune and infectious disease, while also suggesting that targeted intervention may lead to new therapeutic opportunities.¹⁶ Whether these indirect predictive biomarker candidates can ultimately be clinically validated and developed into robust IVDs which will be approved as codeveloped diagnostics in nononcology indications remains to be determined.

Another challenge encountered with many nononcological diseases is the timing of the clinical efficacy study. The earliest clinical efficacy of a therapeutic subgroup of patients tested is in phase II studies since the phase I studies in these indications are often done in healthy volunteers. As such, there is very limited time after phase II to establish and clinically validate these subgroups of patients defined by assay result prior to launch of the therapeutic without delaying the approval and availability of the drug. A successful co-launch of the therapeutic and the diagnostic test depends on many factors, but one key factor is establishing clinical utility, where the test use results in improved treatment decision-making and thereby improved clinical outcome for the patient.¹⁷ The value the diagnostic brings to the overall clinical practice should be clear to the physicians and regulators. The current practice of two independent phase III studies (as required in many therapeutic areas outside of oncology) using a novel diagnostic test may not be sufficient to change clinical practice. It is therefore beneficial to start considering the clinical utility of a novel diagnostic test early in clinical development to allow time to generate additional data that can support physician education and health economic analyses on the potential clinical utility of the test.

If patient subgroups can be reliably identified using established clinical features or existing diagnostics, then developing a novel diagnostic test (either companion or complementary) may not be required, although clinical utility will still need to be established. For example, peripheral blood eosinophil counts were used to enrich for patients with eosinophilic asthma in the pivotal clinical studies with mepolizumab (NUCALA) and reslizumab (CINQAIR), both antiinterleukin-5 (IL-5) antibodies.^{18–22} Blood eosinophil counts are a routine clinical assessment (complete blood count with differential, or CBC-D) and are directly linked to levels of the growth and survival factor IL-5, which is the target of these drugs. No specific companion or complementary assay was considered necessary, allowing physicians considerable flexibility both in testing prospective patients and for classifying patients as falling under an eosinophilic phenotype. There's additional flexibility in the test hardware, software, and threshold of eosinophil number to assign asthma as being of eosinophilic status.

Despite the many challenges present for nononcological indications, it is widely recognized that many of these complex disorders are of heterogeneous pathogenesis and therefore patients will greatly benefit from more targeted therapies and a personalized health care approach.

Strategic considerations

In the context of personalized healthcare, in the past decade the focus in the pharmaceutical industry has been on codeveloping companion diagnostics as a prerequisite for therapeutic approval if the therapy is targeted for a specific population. With the recent addition of complementary diagnostics as an alternative tool to develop successful therapies, the question arises as to what strategy to use for which therapeutic? Should potential options to restrict pivotal drug trial enrollment to only patients selected based on diagnostic testing be considered, if this approach may preclude the ability to support a complementary diagnostic strategy? What are the advantages and disadvantages of a strategy on one end of the spectrum, where only diagnostic assay-positive patients are selected for the trial, which may enable a companion diagnostic, vs. the other end of the spectrum, where an all-comer patient enrollment approach enables a complementary diagnostic option? This question arises early in clinical development, as it may impact the overall clinical development plan, including the clinical trial design and regulatory strategy. Furthermore, it will likely have implications for patient access, as well as the commercial strategies for both the pharmaceutical and the diagnostic companies.

Clinical trial design considerations

An all-comer patient enrollment strategy with or without biomarker stratification and retrospective assessment of status relative to a specific assay could enable either companion or complementary diagnostic assay status upon FDA review of the submission new drug application (NDA)/biologics license application (BLA) and premarket approval (PMA) packages. Based on the nivolumab and atezolizumab approvals for non-small cell lung cancer (NSCLC) as a life-threatening disease with a serious unmet medical need, the primary consideration would likely be not restricting patients to therapy use based on favorable benefit/risk ratio relative to chemotherapy standards of care, thus defaulting to complementary diagnostic status of the assay if the trial succeeds. Thus, diagnostic test-negative patients would also benefit based on submitted data relative to concurrently available therapies. However, for future approvals in any therapeutic area, positive test results in a subgroup using this design may result in companion diagnostic approval if the patients testing negative did not exhibit a favorable benefit/risk ratio relative to standards of care and/or unmet medical need. Conversely, selection of test-positive patients in pivotal studies (i.e., only enrolling test-positive patients) might enable FDA designation of companion diagnostic status if the trial was positive, but would likely not allow for complementary diagnostic status.

Specimen types and platform considerations

The currently approved complementary diagnostics are focused on a single analyte (PD-L1) and on an IHC platform for NSCLC, bladder, or melanoma cancer patients. Similarly, the vast majority of approved companion diagnostics are tests using tumor tissue as the sample type, with either IHC or qPCR as the platform, with the exception of the Ferriscan MRI imaging assay for EXJADE (**Table 2**).

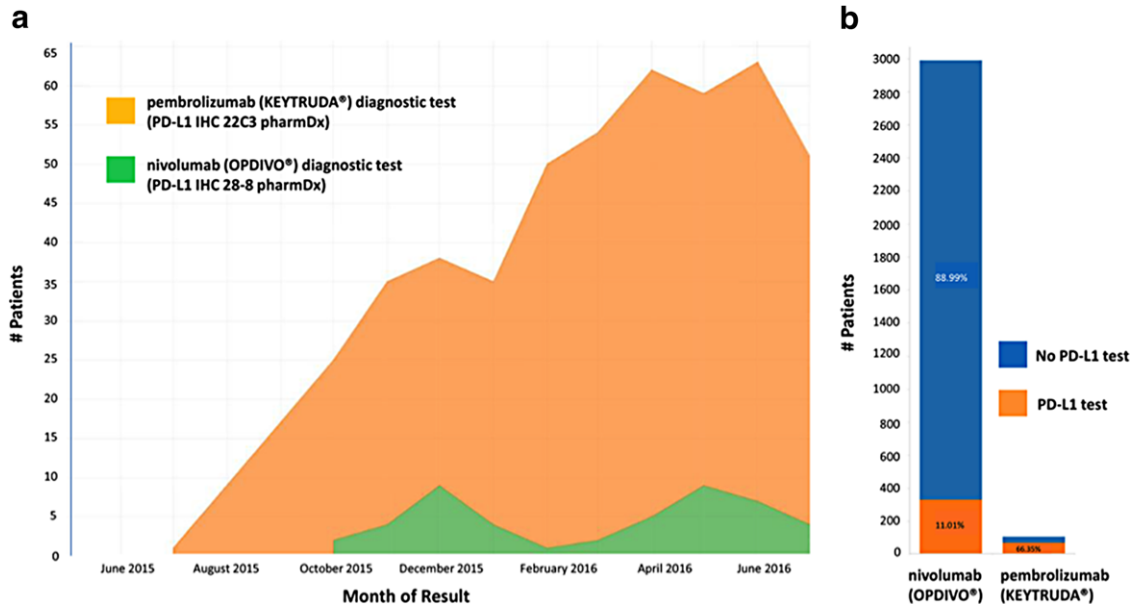


Figure 2 Impact of companion and complementary diagnostic status on (a) use of diagnostic test and (b) use of drug in advanced NSCLC. Data from Flatiron Health database 31 July 2016.

Since the risk/benefit ratio of testing is lower for sampling circulating specimens than taking biopsies, this is an attractive alternative for patients and their physicians for companion and complementary diagnostics to be used for chronic diseases to inform on the potential for greater benefit and enhance the overall treatment dialog between patient and physician. There is significant appeal for using levels of circulating analytes or proteins, such as FDA-approved cell-free DNA (cfDNA) tests for NSCLC patients receiving epidermal growth factor (EGFR) inhibitors such as erlotinib and germline DNA to guide treatment decisions in other diseases such as cystic fibrosis (e.g., ivacaftor), as well as metabolic, cardiovascular, and diseases with immune mechanisms to guide treatment decisions.

The likelihood of a broad use of specific tests would be increased if the tests could show utility across a drug class and if they measured more than one relevant biomarker rather than a single molecular entity or analyte. This concept and accompanying FDA requirements may be nearing approval, with both Foundation Medicine and Illumina aiming for a “universal companion diagnostic” for next-generation sequencing (NGS) panels via FDA approval for oncology indications in the near future. This would represent the first time a multiplex/multimarker test received IVD approval as a companion diagnostic for multiple therapies,²³ albeit as follow-on companion diagnostics rather than as codeveloped tests. This would provide a basis with which to better understand what criteria might be applied to these multiplex NGS-based tests with respect to analytical validation, clinical validation, and clinical utility. The very recent approval of the FoundationFocus CDxBRCA test for rucaparib is an example of an NGS-based companion diagnostic for two genes on separate chromosomes. (BRCA1 on 17q and BRCA2 on 13q). Global platform-installed base and global access to specific testing technologies are also important considera-

tions for pharmaceutical and diagnostic companies codeveloping therapies and assays. IHC, for example, has very high global availability, even in emerging markets, while NGS holds great promise for universal companion diagnostic testing, and adoption of the technology is growing and is currently more centralized in many regions.

Reimbursement and commercial considerations

For pharmaceutical and diagnostic sponsors codeveloping therapies with their respective tests, the prospect of developing and launching a complementary diagnostic provides the opportunity to increase access of the therapy to all patients and not restrict it to a specific biomarker subgroup based on test results. In the complementary diagnostics scenario, with a corresponding therapy that has demonstrated all-comer benefit, the path to establishing clinical utility of the test may be more complex than for a companion diagnostic test. As described in BEST,¹ the widely accepted definition of clinical utility for an assay is the conclusion that a given use of a medical product will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management, or prevention of a disease. Clinical utility includes the range of possible benefits or risks to individuals and populations. In the context of medical community uptake or health economics, the concept of clinical utility may often also be used to encompass effectiveness and/or economic implications including uptake, coverage, and reimbursement. The preliminary evidence to date, based mainly on testing for previously treated NSCLC, suggests that physicians may order complementary diagnostics far less frequently than companion diagnostic tests on a per-patient basis. This is illustrated in **Figure 2a** via Flatiron data, based on a July 2016 snapshot, which shows nivolumab (OPDIVO), an anti-PD-1 antibody approved for all-comers with a complementary

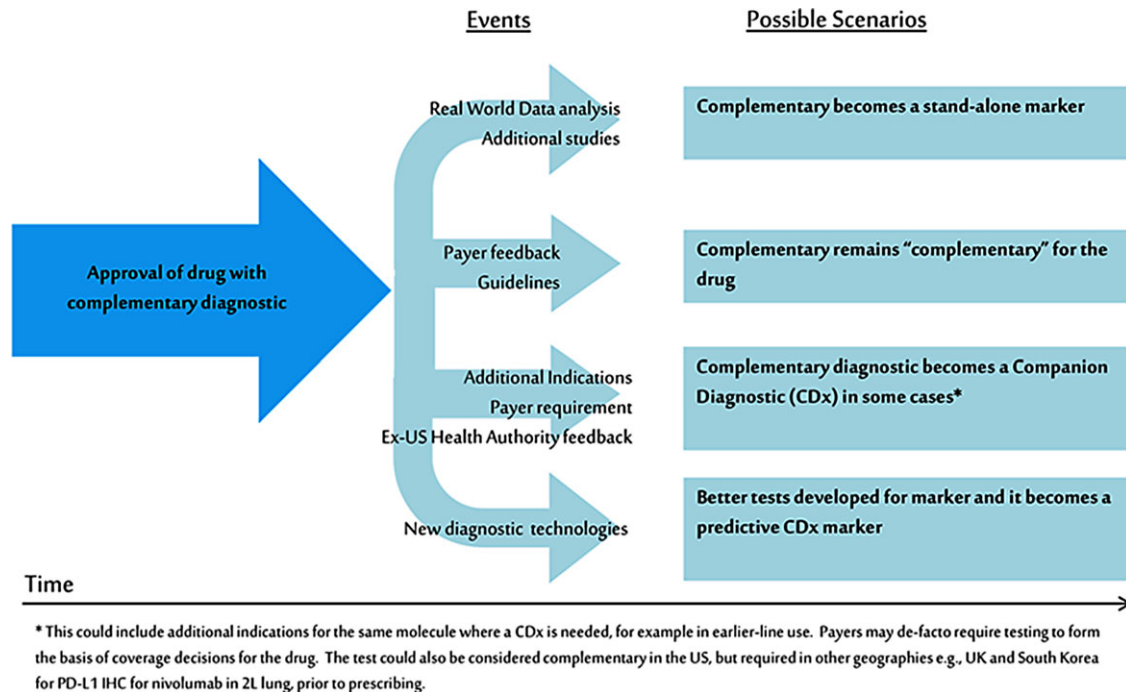


Figure 3 Potential commercial strategies of evolving Complementary Diagnostics.

diagnostic status. In terms of testing volume, it is apparent that the pembrolizumab (KEYTRUDA) diagnostic test (PD-L1 IHC 22C3 PharmDx) is used much more than the nivolumab (OPDIVO) diagnostic test (PD-L1 IHC 28-8) relative to the total number of patients treated with each drug, due to the difference in “need-to-test” status for a companion vs. the “no-need-to-test” complementary diagnostic. However the drug nivolumab (OPDIVO) was prescribed to more patients than pembrolizumab (KEYTRUDA) (**Figure 2b**). Also, as of July 2016, this emerging data showed that the complementary diagnostic PD-L1 28-8 IHC assay codeveloped for nivolumab (OPDIVO) was used much more frequently overall in NSCLC than the companion diagnostic 22C3 PD-L1 IHC assay pembrolizumab (KEYTRUDA) (also an anti-PD-1 antibody), which is approved with a restricted label for patients with elevated expression of PD-L1 in their tumor tissue (**Figure 2b**). Importantly and for relevant context, this July 2016 snapshot of PD-L1 IHC testing reflects only the complementary vs. companion status in the United States only, where neither nivolumab (OPDIVO) nor atezolizumab (TECENTRIQ, approved in October 2016) are restricted by either payers or the FDA based on PD-L1 status in previously treated NSCLC. Testing practices for PD-L1 IHC in cancer patients, particularly for NSCLC, are still evolving outside the United States.

Outside of the United States, examples are emerging of payers utilizing the results of complementary testing to limit patient eligibility for reimbursement based on financial considerations. For example, in both the United Kingdom and South Korea, nivolumab (OPDIVO) is only reimbursed for high expressors of PD-L1 protein via IHC testing, thus acting as a *de facto* companion diagnostic from a payer and access perspective. This contrasts with its complementary diagnostic

status determined by the FDA in the United States, where no patients are restricted from receiving this therapy. Similarly, stand-alone diagnostics (tests that provide information to patients on disease or physiological status that are not linked to a specific drug) can also evolve to companion and potentially complementary use if subsequently linked to a therapeutic. An excellent example of this is the Myriad BRACAnalysis CDx test, initially available as a stand-alone diagnostic test for assessment of risk for developing hereditary cancers. This test was subsequently used in clinical studies approved by the FDA via the PMA route as an approved diagnostic device that detects and classifies mutations in the *BRCA1* and *BRCA2* genes, using genomic DNA obtained from whole blood samples from a patient, as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with olaparib (LYNPARZA).

Only FDA-approved or FDA-cleared tests have the opportunity to come to market with data already available regarding the clinical utility of the test. Further assessment of clinical utility of an assay in the community may require additional capture of real-world evidence, and challenges in achieving this goal in the postapproval setting may vary among companion and complementary diagnostics.

As shown in **Figure 3**, commercial strategies may evolve in the United States following initial determination of complementary diagnostic status. For example, complementary diagnostic status in the United States may evolve to companion diagnostic status in other geographic regions. Specifically, as now seen for nivolumab, in previously treated NSCLC in the United Kingdom and South Korea a positive test status is required to ensure reimbursement for treatment. Another scenario laid out in

Figure 3 is that following initial complementary diagnostic approval, a follow-on diagnostic approval using an improved platform may occur. This is a likely future scenario for cancer immune therapies, with the aspiration of future comprehensive cancer immune panels at diagnosis that could capture key information on oncogene activation, mutational load, and gene expression. Overall, these could replace the current practice of separate tests and extensive tissue sources for PD-L1 IHC, EGFR testing, etc.

Recognizing that the experience with FDA complementary diagnostics is still limited in the United States, many questions remain as to further evolution of this field, on topics ranging from clinical development to regulatory approval, commercial launch, and post-launch status. Since the current examples are limited to a single analyte and platform (PD-L1 IHC) and only two tests, the potential for expansion is significant. It is worth considering potential future additions to this short list of approved complementary diagnostics, such as tests for immune status in the nononcology space.

SUMMARY

In conclusion, predictive biomarkers help in identifying patient subgroups that are most likely to derive clinically meaningful benefit while reducing the risk of unnecessary exposure and cost to patients who would not benefit. Companion diagnostics can be codeveloped with therapeutics, and are used to identify and restrict treatment only to those responder subgroups of patients. Complementary diagnostics are a relatively recent new tool that are not required for the safe and effective use of a therapeutic but can further aid physicians in the benefit–risk decision-making about the use of a therapeutic (for instance, by identifying patients who may be relatively more likely to derive benefit). Although to date there are limited precedents for complementary diagnostics, these may be another useful tool to help guide medical practice as it is likely that in the future more diagnostic-partnered drugs will be launched.

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