We define a companion diagnostics (CDx) test as any diagnostic tool that guides the selection of patient treatment. In the US, these tests include diagnostics cleared by the Food and Drug Administration (FDA), as well as laboratory-developed tests (LDTs) run in CLIA-accredited laboratories. The answer to the title’s question is obviously in the affirmative. We discuss the growing need to improve, accelerate, and standardize oncology CDx that benefit patients. Recent advances in our understanding of the mutational landscape of cancers have led to the rapid development of targeted therapies for pathogenic targets. At the same time, advances in next-generation sequencing (NGS) have revealed the complexity of heterogeneous cancers. With the fast pace of change occurring in clinical oncology, flexible approaches to CDx development are needed while test accuracy is maintained for delivering precision medicine to patients.

The remarkable efficacies of new targeted therapies have recently changed the paradigm for oncology to one of matching the right patient with the right therapy (1). This approach requires robust laboratory testing of patient samples. FDA-cleared tests exist for a limited number of markers (Table 1). In contrast, LDTs developed in CLIA-certified laboratories are used for >2000 genetic tests (2). LDTs are currently used in oncology for patient care and in clinical trials, which are now evaluating >500 agents targeting >100 genomic alterations.

The recent success in the development of 2 targeted therapies, crizotinib and vemurafenib, exemplifies the CDx process in which the FDA has co-cleared a diagnostic test (3, 4). The development of the CDx included analytical validation and elements of quality systems (good manufacturing practice, design control, personnel, software, instrumentation, and other parameters) as critical components of the regulatory package. The tests were used to recruit patients to pivotal phase II trials for the presence of the mutation/gene fusion. The clear clinical response observed in patients treated with the novel therapies provided clinical validation of the drugs and the diagnostic tests. The drug clearance included the CDx package of analytical validation, adherence to quality systems regulation, and the clinical-validation data package. On the other hand, the FDA’s refusal to clear omacetaxine for targeted T315I mutation–positive chronic myelogenous leukemia was based on a failure to show interlaboratory concordance, which can lead to misclassification of patients and potential risk.

In contrast to these examples, CDx development for anti-epidermal growth factor receptor (EGFR) antibody therapies in colorectal cancer highlights the evolving landscape of precision medicine. Tumor production of EGFR, as measured by immunohistochemistry with an FDA-cleared CDx test, was used to select patients for pivotal phase III trials of cetuximab and panitumumab; however, the detection of EGFR protein expression was later discovered to be variable and not to demonstrate clinical utility (5). This result quickly led to the use of panitumumab and cetuximab without testing for EGFR protein expression. Meanwhile, cetuximab and panitumumab were discovered to be effective only when the wild-type KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) gene is in the tumor (6, 7). After these data emerged, European and American Society for Clinical Oncology guidelines recommended testing for KRAS mutation with LDT-based tests to exclude patients harboring KRAS mutant tumors before initiating therapy. Despite the almost universal clinical practice of KRAS mutation testing for colorectal cancer over the past 4 years, an FDA-cleared CDx for KRAS became available only this year for use in EGFR antibody therapies. Notably, the need to test for EGFR protein expression before anti-EGFR antibody therapy remains on the drug label.

Complexity like that observed for colorectal and lung cancer is likely to be seen again with the increasing

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Nonstandard abbreviations: CDx, companion diagnostics; FDA, US Food and Drug Administration; LDT, laboratory-developed test; NGS, next-generation sequencing; EGFR, epidermal growth factor receptor.

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6 Human genes: KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; HER2, human epidermal growth factor receptor 2; current symbol and name: ERBB2, v-erb-b2 erythroleukemia viral oncogene homolog 2, neural/glioblastoma derived oncogene homolog (avian); BRAF, v-raf murine sarcoma viral oncogene homolog B1; BCR, breakpoint cluster region; ABL, c-abl oncogene 1, non-receptor tyrosine kinase; ALK, anaplastic lymphoma receptor tyrosine kinase.
understanding that cancers are heterogeneous, harbor multiple mutations, and rapidly acquire changes that lead to resistance to targeted therapies (8–10). To address this heterogeneity and the resistance to targeted therapy, the FDA is encouraging the development of combination therapies. To achieve this goal requires the rapid development of CDx for measuring multiple genetic markers; however, the current drug–CDx development framework is not optimized to harness and apply our rapidly evolving knowledge of cancer subtypes. We suggest that the development of CDx for oncology agents, especially those targeted to specific genetic alterations, requires an improved process when the evidence for clinical efficacy is compelling.

In the US, FDA-cleared CDx tests are performed in CLIA-certified laboratories that use the same test across laboratories and in accordance with manufacturer instructions. In addition, CLIA-certified laboratories can develop their own LDTs. The requirements for an LDT are substantially different from an FDA-cleared test. CLIA certification establishes that the laboratory is certified to perform clinical laboratory testing; however, the individual LDTs performed in a given laboratory are not necessarily monitored by CLIA. In contrast, FDA clearance of CDx tests is subject to regulation to ensure that the test performs reproducibly across laboratories and demonstrates clinical utility (Table 2). LDTs are developed rapidly in response to medical advances and fill a void when no FDA-cleared test is available, but LDTs may lack adequate test validation (11). Owing to these differences, a gap may result in optimal matching of the right patient to the right drug when medical practice changes rapidly. Thus, changes to the system are essential for enabling rapid translation of scientific evidence into high-quality clinical practice and thereby improvements in patient care.

| Table 1. Select list of CDx used for selection of targeted therapies.\(^a\) |
|---|---|---|---|---|---|
| **Biomarker** | **Type** | **Year of clearance** | **Drug** | **Indication** |
| **KRAS** mutation | LDT\(^b\) | 2006 | Cetuximab, panitumumab | Colorectal cancer |
| | PMA | 2012 | | |
| **BRAF V600E** mutation | PMA | 2011 | Vemurafenib | Melanoma |
| **ALK fusion** | PMA | 2011 | Crizotinib | NSCLC |
| **EGFR** mutation | LDT | 2003 | Gefitinib, erlotinib | NSCLC |
| **HER2** amplification | PMA | 1998 | Trastuzumab | Breast cancer |
| | PMA | 2008 | | |
| **BCR-ABL** translocation | PMA | 2005 | Imatinib, dasatinib, nilotinib | CML |


\(^b\) LDT, LDT in a CLIA-certified clinical laboratory; PMA, Premarket Approval by the FDA; ALK, anaplastic lymphoma receptor tyrosine kinase (gene); NSCLC, non–small cell lung cancer; CML, chronic myelogenous leukemia.

| Table 2. Comparison of FDA-cleared tests with LDTs developed under CLIA guidelines. |
|---|---|---|---|
| **FDA-cleared test** | **LDT** |
| Regulated by the FDA: All systems used in testing are subject to review (instrumentation, reagents, software, manufacturing, and other parameters) | Regulated under CLIA guidelines and sometimes those of individual states (laboratory procedures, documentation, quality management, work flow, and other parameters) |
| Developed under Quality Systems Regulations | Developed under laboratories’ own quality-management systems |
| Used across many laboratories | Test is used within the laboratory that validates the assay |
| Uniformity of testing across laboratories for the same test by the same manufacturer; however, tests manufactured by different manufacturers may differ | Variations between laboratories in methodology for the same test |
| Manufacturer subject to stringent quality assurance/control as part of the Quality Systems Regulation | Subject to proficiency testing for determining test quality |
We contend that the time has come for CDx governing bodies to address the problem and deliver coherent solutions.

The problem is compounded by the growth in the number of actionable alterations in cancers that might lead to the selection of the most appropriate therapy for a patient, for both approved and experimental drugs. An additional challenge with the increased number of relevant markers is the amount of tumor tissue available from a patient [i.e., “tissue is the issue” (12)]. Repeated testing of tumor samples quickly depletes the sample before the appropriate test can be performed to match the patient with the right therapy. Therefore, using multiplex testing for a comprehensive analysis of all the actionable alterations would provide maximal benefit to the patient. Recognition of this need has prompted growth in the use of NGS tests in CLIA-certified laboratories for measuring mutations in tumors for hundreds of genes (13). Challenges remain for NGS as a diagnostic technique, including standardization of instrumentation, preanalytical variables for formalin-fixed tissues, and data interpretation. The necessary extent of NGS data coverage and the robustness of the analytical pipelines for identifying gene mutations will continue to be refined and in turn will accelerate the definition of the clinical utility of specific mutations.

Variation in test results can be due to differences in instrument/assay characteristics, interlaboratory procedures, and biological variation (14, 15). Each of these parameters leads to imprecision in CDx performance. Examinations of the variation in FDA-cleared tests for the estrogen receptor 1 protein and for HER2 [human epidermal growth factor receptor 2; current name: ERBB2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)], Braf [v-raf murine sarcoma viral oncogene homolog B1], and other genes have revealed large interlaboratory and intrapatient discordance (5%–20%). Although improvements in test performance evolve over time as tests are adapted in clinical practice—even after FDA clearance—earlier introductions of tests into clinical settings can accelerate the process.

Given the rapid changes in science and medicine and the global development of new drugs, flexible options for CDx development will benefit patients. Many possible alternative approaches may be appropriate to bridge the current gap between CLIA and the FDA in the availability of tumor diagnostic tests while maintaining high standards of quality and reproducible results. Such approaches would leverage the respective strengths of the regulatory environment and the clinical laboratory in the development of CDx. Some of these approaches could include increasing proficiency testing to increase accuracy and minimize interlaboratory variation in LDT results. Alternatively, it would be highly desirable to have a mechanism for facilitating the rapid availability of commutable calibrators and standards that serve as external quality controls for the assay, as has been proposed for BCR-ABL (breakpoint cluster region—c-abl oncogene 1, non-receptor tyrosine kinase) transcript-level quantification (16). Other possibilities for CDx could include the FDA de novo 510(k) process, which allows investigation of a test’s analytical validity before the clinical utility of a therapy has been established. Also important would be any flexible approach for including the development of a multigene approach via such technologies as NGS, which would be cost-effective alternatives to the current practice of repeated single-gene testing. Not all approaches for developing CDx tests should be treated equally, however. For example, gene signatures based on transcriptomics and proteomics should be developed with caution, because they are empirically rather than mechanistically associated with the therapy (17).

The rapid pace of medical progress in elucidating the genetic basis of cancers demands that CDx tests use all available paths to ensure the rapid delivery of critical tests that benefit patients. Now is the time to exploit advances in technologies like NGS to develop tests for cancers that measure multiple mutations with a single sample. The development of rational approaches to test development, test validation, and the delivery of high-quality and useful information to patients will have a tremendous positive impact on health outcomes. Delaying this future through overly stringent regulatory approaches will slow the progress of precision medicine around the world.

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References