special articles

Missing Companion Diagnostic for US Food and Drug Administration–Approved Hematological and Oncological Drugs

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abstract

Within hematology and oncology, companion diagnostics (CDxs) play an increasing role in securing an optimal therapy for individual patients, and the US Food and Drug Administration (FDA) consider this type of assay essential for the safe and effective use of a corresponding therapeutic product. Most CDxs are developed prospectively using the drug-diagnostic codevelopment model, which normally secures the simultaneous approval of both drugs and diagnostics. A CDx assay is an important treatment decision tool that needs to be available simultaneously with the drug. However, within the past few years, several targeted drugs and new indications have been approved by the FDA without a CDx, despite the use of a predictive biomarker assay for patient selection during clinical development. A missing analytical and clinically validated CDx assay could affect the correct use of these drugs and ultimately patient safety. An alternative to FDA-approved or FDA-cleared CDxs could be to use a laboratory-developed test, which will normally miss documentation on the clinical validity. On the basis of the information available from different publicly available FDA databases, this article briefly discusses the issue of missing CDx assays in relation to the approval of hematological and oncological drugs and new indications.

JCO Precis Oncol 6:e2200100. © 2022 by American Society of Clinical Oncology

INTRODUCTION

For more than two decades, companion diagnostics (CDxs) have played a significant role in the development of targeted drugs in hematology and oncology. However, these assays are critical not only during the drug development phases. They are just as critical after the regulatory approval of the drug, where they act as important treatment decision tools. In fact, many of the current targeted drugs would lose their value without a CDx assay. The first drug ever to obtain US Food and Drug Administration (FDA) approval together with a CDx assay was the monoclonal antibody trastuzumab.[1] In 1998, trastuzumab was approved for the treatment of human epidermal growth factor receptor 2–positive metastatic breast cancer, together with the immunocytochemical assay HercepTest.[2] Since then, the number of hematological and oncological drugs that have a CDx assay linked to their use has increased substantially. At the beginning of 2022, the FDA has determined that a CDx assay is essential for the safe and effective use of more than 50 drugs. However, within the past few years, we have experienced that the FDA has approved targeted drugs and new indications without a CDx assay, although predictive biomarker assays were used during clinical development to select likely responding patients. A missing analytical and clinically validated CDx assay could have an impact on the correct use of these drugs and ultimately patient safety. In this article, the issue of missing CDx assays in relation to the approval of new drugs and indications will be discussed. For this discussion, information was extracted from different publicly available FDA databases, including the Table of Pharmacogenomic Biomarkers in Drug Labeling, List of Cleared or Approved Companion Diagnostic Devices, Drugs@FDA: FDA-Approved Drugs, Postmarket Requirements and Commitments, and Post-Approval Studies Database.[3-7]

FDA REGULATIONS FOR CDx

The FDA defines a CDx assay as an in vitro diagnostic device that provides information essential for the safe and effective use of a corresponding therapeutic product.[8] This definition originates from a guidance document issued by the FDA in 2014, where it is further stated that an inadequate performance of a CDx assay can have severe therapeutic consequences for the individual patient as erroneous results could lead to withholding appropriate therapy or administration of inappropriate therapy. Consequently, the FDA classifies CDx assays as high-risk class III devices, which require submission of substantial documentation for both the analytical and clinical performances before the assay can be approved and

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Accepted on May 4, 2022 and published at ascopubs.org/journal/po on June 16, 2022: DOI https://doi.org/10.1200/PO.22.00100

CONTEXT

Key Objective

In the past few years, several targeted hematological and oncological drugs and new indications have been approved by the US Food and Drug Administration (FDA) without a companion diagnostic (CDx), despite the use of a predictive biomarker assay for patient selection during clinical development.

Knowledge Generated

A review of various publicly available databases at the FDA has shown that within the past 5 years, at least 10 targeted drugs and new indications have been approved without a CDx being available at the time of approval. In this situation, the FDA postmarket requirements will include the development of an assay. However, for two new indications approved 5 years ago, the review showed that CDx assays are still not available.

Relevance

A missing analytical and clinically validated CDx assay could influence the correct use of targeted hematological and oncological drugs and ultimately patient safety.

used in the clinic. It is further stated that if the FDA determine that a CDx assay is essential to the safe and effective use of a new drug or indication, they will not approve the drug or indication if an assay is not simultaneously approved. However, the guidance document states that during product review, the FDA may open up to waive this rule in specific situations.[8]

Such a situation could be for a new drug intended to treat serious or life-threatening conditions. Here, the FDA may decide to approve the drug even if a CDx assay is not yet approved or cleared, if no satisfactory alternative treatment exists. However, the benefits from the use of the drug should be so pronounced that it outweighs the risks caused by the lack of an approved or cleared CDx assay. Another situation could be for an already approved drug, in the case of a new indication. Here, the FDA will normally not approve the new indication and update the labeling for the drug until the CDx assay is approved or cleared. However, the FDA recognizes that there may be occasions when the labeling for an already approved drug must be revised to address a serious safety issue. Under these circumstances, if the benefits from the use of the drug are so pronounced that it outweighs the risks caused by the lack of an approved CDx assay, the FDA does not intend to delay approval of changes to the labeling of the drug until the assay is approved.[8] However, in both situations, the FDA expects the applicant to submit an application for a CDx assay, and in the New Drug Application (NDA) or Biologics License Application (BLA) Approval Letter, an expected submission deadline is stipulated.[8]

Looking at the CDx assays so far approved by the FDA, the majority of these are developed contemporaneously with the drug using the prospective drug-diagnostic codevelopment model.[9] On the basis of a thorough molecular understanding of the pathophysiology and mechanism of action of the drug, a predictive biomarker assay is developed and used to enrich the clinical trial populations with likely responding patients. This model increases the power of the individual clinical trials and the likelihood of a successful outcome as well as a simultaneous regulatory approval of both drug and diagnostic.[10,11] In 2016, the FDA issued a draft guidance document on drug-diagnostic codevelopment, and here, they discussed an alternative study design for the clinical validation of CDx assays, the prospective-retrospective study design.[12] Using this design, a prospective collection of specimens is performed from the patients enrolled in the clinical trial with the drug for which the CDx assay is to be developed. After completion of the clinical trial, the collected specimens will be tested with the subsequent developed CDx assay, and the results are then analyzed retrospectively. Although most CDx assays are developed using a prospective study design, there are possibilities for a retrospective development if specimens and clinical outcome data are available from the therapeutic clinical trial. However, using a prospective-retrospective study design can be challenging if an insufficient number of biomarker-positive patients are enrolled in a prospectively conducted clinical trial.[12]

On the basis of a review of the different FDA databases listed in the Introduction, 52 hematological and oncological drugs were identified as having an FDA-approved or FDA-cleared CDx assay linked to their use.[3-7] In addition, the review also revealed four additional drugs and six new indications approved without a CDx assay, despite a predictive biomarker assay had been used for patient selection during clinical development. Figure 1 illustrates the cumulative number of FDA-approved CDx-drug combinations in hematology and oncology from 1998 to the present. The figure also includes the drugs and new indications approved by the FDA without a CDx assay.

NEW TARGETED DRUGS WITHOUT AN FDA-APPROVED CDx

The four drugs that have been approved without a CDx assay are entrectinib, avapritinib, selpercatinib, and tepotinib and are listed in Table 1. After the identification of

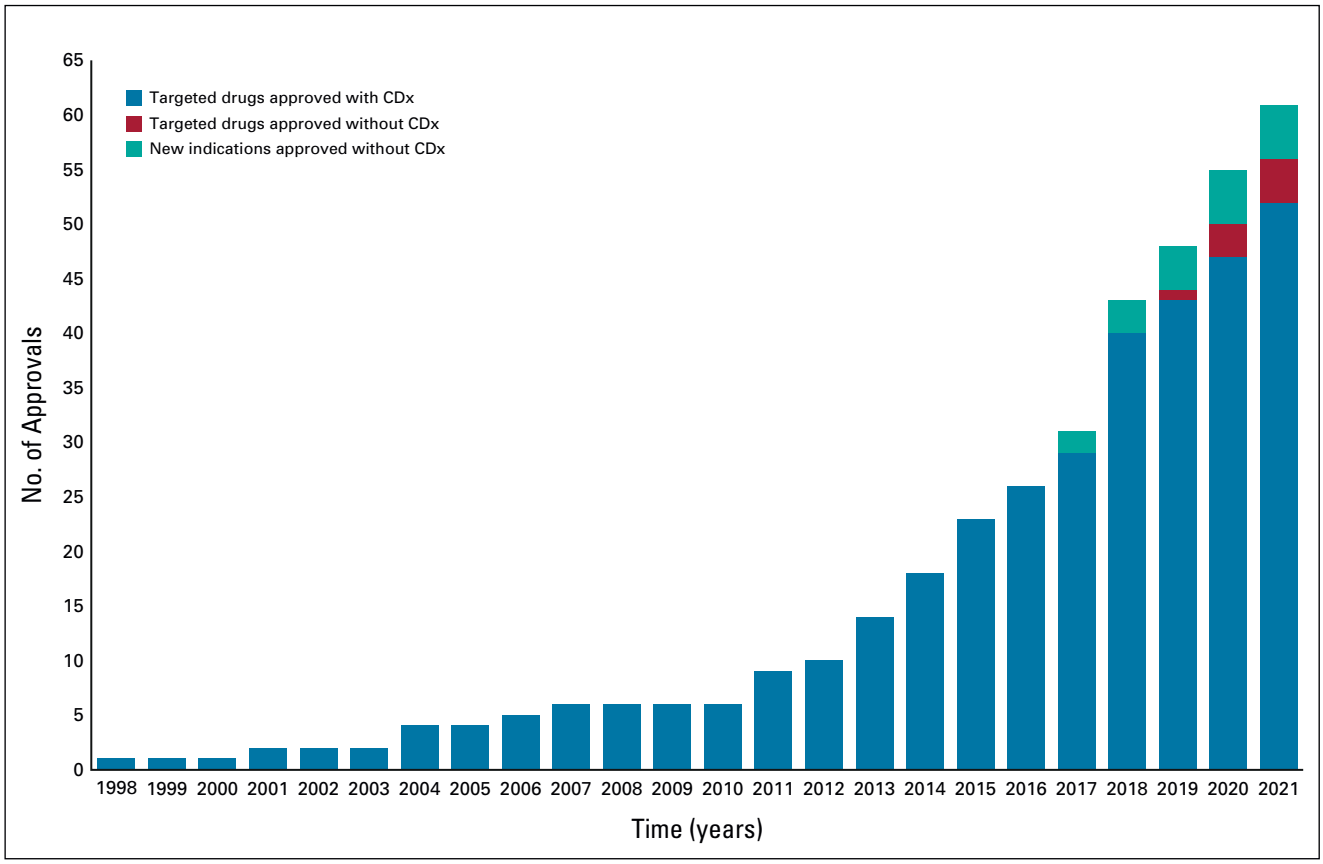

FIG 1. The cumulative number of US Food and Drug Administration–approved CDx-drug combinations within hematology and oncology from 1998 to present. The figure also includes new drugs and indications that have been approved without a CDx assay. CDx, companion diagnostic.

these drugs, their Full Prescription Information and NDA Approval Letters were reviewed.[5] For these drugs, no analytical and clinically validated CDx assay was available at the time of drug approval, despite the clinical trials had all used one or more predictive biomarker assays for patient selection. In the Full Prescribing Information for all four drugs, under the section Dosage and Administration, information is available on how the patients must be selected, and here, it is stated that an FDA-approved assay is currently unavailable. In the Approval Letters for these drugs, the FDA have included a paragraph on postmarketing commitments, including a commitment to develop a CDx assay for the identification of patients who might benefit from the drug in question. An expected timeline for the final regulatory submission of the CDx assay is also included. Furthermore, the databases on Postmarket Requirements and Commitments and Post-Approval Studies were checked to retrieve a status of the different commitments. This information is presented in Table 1.

One of the drugs listed in Table 1 is entrectinib, a multikinase inhibitor that inhibits TRK, ROS1, and ALK.[13] In 2019, entrectinib obtained FDA approval for the treatment of patients with solid tumors harboring neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusion and for patients with non–small-cell lung cancer whose tumors were *ROS1*-positive.[14] In the clinical trials that led to the approval of entrectinib in patients with solid tumors, the *NTRK* fusion–positive status was determined by various nucleic acid–based tests, either at local or central laboratory facilities. The situation was the same for the identification of *ROS1* rearrangements in patients with non–small-cell lung cancer. In August 2019, at the time of FDA approval, no analytical or clinically validated CDx assays for the detection of *NTRK* gene fusion and *ROS1* rearrangements were available. The text extracted from the NDA Approval Letters for entrectinib on the postmarketing commitments for CDx assay development is shown in Table 1.[15,16] The timetable in the Approval Letters for the regulatory submissions was December 2019, and according to the FDA List of Cleared or Approved Companion Diagnostic Devices, no *NTRK* or *ROS1* assays have yet been approved for entrectinib at the beginning of 2022. However, according to the database for Postmarket Requirements and Commitments, applications for both assays have been submitted to the FDA but have not yet been approved. The situation is similar for the three other drugs listed in Table 1. In addition to entrectinib, it is only for avapritinib that the timetable in the Approval Letter indicates that a CDx assay could have been approved by now.

TABLE 1. Targeted Drugs Without an US Food and Drug Administration–Approved Companion Diagnostic

Drug	Biomarker(s)	Approval	Postmarketing Commitments/Submission Date/Status for Submission
Entrectinib (Rozlytrek)	*ROS1* rearrangement *NTRK* gene fusion	August 2019	1. Commit to providing adequate analytical and clinical validation results (b) (4) from clinical trial data to support labeling of the test to detect *ROS1* rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for the ROS1 indication. The clinical validation should be supported by a clinical bridging study comparing (b) (4) and the clinical trial enrollment assays. *Submission date: December 2019* *Status of submission: submitted but not approved* 2. Commit to providing adequate analytical and clinical validation results from clinical trial data to support labeling of the F1CDx test to detect *NTRK* rearrangements for identifying patients who may benefit from entrectinib. *Submission date: December 2019* *Status of submission: submitted but not approved*
Avapritinib (Ayvakit)	*PDGFRA* exon 18 mutations	January 2020	Develop and submit the report of a valid CDx to detect *PDGFRα* D842V somatic variants for identifying patients with GIST who may benefit from avapritinib using clinical trial data from study BLU-285-1101 *Submission date: December 2020* *Status of submission: submitted but not approved*
Selpercatinib (Retevmo)	*RET* gene fusion *RET* mutations	May 2020	1. Submit the final report of an analytical and clinical validation study using clinical trial data that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with RET gene fusions in non–small-cell lung cancer. *Submission date: December 2021* *Status of submission: submitted but not approved* 2. Submit the final report of an analytical and clinical validation study using clinical trial data that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of selpercatinib for patients with *RET* gene fusion–positive thyroid cancer and *RET* mutation–positive medullary thyroid cancer. *Submission date: May 2022* *Status of submission: submitted but not approved*
Tepotinib (Tepmetko)	*MET* exon 14 skipping	February 2021	Submit a summary of the final report of an analytical and clinical validation study using clinical trial data that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of tepotinib for patients diagnosed with non–small-cell lung cancer, whose tumors harbor *MET* exon 14 skipping. *Submission date: January 2022* *Status of submission: pending*

NOTE. The table included extracted text from the Full Prescribing Information and the New Drug Application Approval Letter.[5]
Abbreviations: CDx, companion diagnostic; GIST, gastrointestinal stromal tumor.

For more information on the different drugs, please refer Table 1, and information is available in Drugs@FDA: FDA-Approved Drugs and the database for Postmarket Requirements and commitment.[5,6]

NEW INDICATIONS FOR TARGETED DRUGS WITHOUT AN FDA-APPROVED CDx

Several targeted hematological and oncological drugs are approved for more than one indication, which in some instances requires the use of different CDx assays to select the right patient population for treatment. The monoclonal anti–programmed death-1 antibody pembrolizumab is such a drug, which is currently approved for 19 different indications, and for approximately half of these, testing with a CDx assay is required.[17,18] In addition to programmed cell death ligand 1 expression, it is testing for tumor mutational burden high, microsatellite instability high (MSI-H), and mismatch repair deficiency (dMMR). A review of the different FDA databases listed in the Introduction revealed four different oncological drugs with six new indications approved without the simultaneous approval of CDx assays. Table 2 lists these drugs, their indications, postmarketing commitments, and status of submission. In addition to pembrolizumab, it is new indications related to dabrafenib, trametinib, and pralsetinib.

As shown in Table 2, pembrolizumab accounted for three of the six new indications that were missing an FDA-approved CDx assay and were all related to the MSI-H and dMMR biomarkers. In 2017, pembrolizumab was approved for the treatment of patients with unresectable or metastatic solid tumors with MSI-H or dMMR, which in fact was the first tumor-agnostic indication approved by the FDA.[18] This approval was granted without CDx assays for the detection of the two biomarkers. In the clinical trials that led to the approval of pembrolizumab for this indication, patients

TABLE 2. New Indications for Already Approved Targeted Drugs Without an US Food and Drug Administration–Approved Companion Diagnostic

Drug/Indication	Indication	Biomarker(s)	Approval	Postmarketing Commitments
Pembrolizumab (Keytruda)	Unresectable or metastatic solid tumors	MSI-H and dMMR	May 2017	1. Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are dMMR. *Submission date: June 2019* *Status of submission: delayed* 2. Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid–based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are MSI-H. *Submission date: June 2019* *Status of submission: delayed*
Pembrolizumab (Keytruda)	Unresectable or metastatic colorectal cancer	MSI-H and dMMR	May 2017	1. Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are dMMR. *Submission date: June 2019* *Status of submission: delayed* 2. Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid–based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are MSI-H. *Submission date: June 2019* *Status of submission: delayed*
Dabrafenib (Tafinlar)	Metastatic ATC	*BRAF* V600E mutations	May 2018	Commitment to establish, through the use of clinical trial data, an in vitro diagnostic device that is essential to the safe and effective use of dabrafenib and trametinib for patients with *BRAF* V600E mutations in ATC tumor specimens. *Submission date: May 2020* *Status of submission: submitted but not approved*
Trametinib (Mekinist)	Metastatic ATC	*BRAF* V600E mutations	May 2018	Commitment to establish, through the use of clinical trial data, an in vitro diagnostic device that is essential to the safe and effective use of dabrafenib and trametinib for patients with *BRAF* V600E mutations in ATC tumor specimens. *Submission date: May 2020* *Status of submission: submitted but not approved*
Pembrolizumab (Keytruda)	Advanced endometrial carcinoma	MSI-H and dMMR	September 2019	1. Commitment to support the availability of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are dMMR proficient through an appropriate analytical and clinical validation study using clinical trial data that will support labeling. *Submission date: September 2023* *Status of submission: pending* 2. Commitment to support the availability of a nucleic acid–based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are not MSI-H through an appropriate analytical and clinical validation study using clinical trial data that will support labeling. *Submission date: September 2024* *Status of submission: pending*
Pralsetinib (Gavreto)	Thyroid cancer	*RET* gene fusion and *RET* gene mutations	December 2020	Submit a summary of the final report of an analytical and clinical validation study using clinical trial data that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of pralsetinib for patients with *RET* gene fusion thyroid cancers and *RET* mutation–positive medullary thyroid cancer. *Submission date: January 2024* *Status of submission: pending*

NOTE. The table included extracted text from the Full Prescribing Information and the Supplemental New Drug Application/Biologics License Application Approval Letter.[5]

Abbreviations: ATC, anaplastic thyroid cancer; dMMR, mismatch repair deficiency; MSI-H, microsatellite instability high.

were enrolled based mainly on local laboratory-developed immunocytochemical and polymerase chain reaction assays. As no analytical and clinically validated CDx assays for the detection of MSI-H and dMMR were available at the time of approval, postmarketing commitments were included in the BLA Approval Letter with regard to the development of CDx assays for the two biomarkers.[19] Part of this text is included in Table 2. Along with the approval of the solid tumor indication, pembrolizumab was approved for another indication that required testing for MSI-H or dMMR, namely unresectable or metastatic colorectal cancer. In addition, for this indication, postmarketing commitments with respect to CDx assay development were included in the Approval Letter. For both indications, the timetable for regulatory submissions to the FDA was June 2019, but according to the *List of Cleared or Approved Companion Diagnostic Devices and the Postmarket Requirements and Commitments* database, no applications for CDx assays have yet been submitted to the FDA.[4,5] In 2019, pembrolizumab was approved for yet another indication where testing for MSI-H or dMMR was required. Here, pembrolizumab in combination with lenvatinib was approved for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR positive.[18] Similar to the two other indications, no analytical or clinically validated assays were available at the time of approval. However, for the endometrial carcinoma indication, the timetable for the fulfillment of the postmarketing commitments with respect to CDx assays was somewhat more liberal as a regulatory submission to the FDA was set for September 2023 for the dMMR assay and September 2024 for the MSI-H assay.

In addition to pembrolizumab, Table 2 lists three other new indications for already approved drugs where an FDA-approved CDx assay was unavailable at the time of approval, and postmarketing commitments were likewise included in the NDA Approval Letters. The anaplastic thyroid cancer indication for dabrafenib and trametinib had an estimated submission date to the FDA as of May 2020, and according to the database for Postmarket Requirements and Commitments, applications have been submitted, but the CDx assays have not yet been approved. For pralsetinib, the submission timetable for thyroid cancer indication is January 2024.[5] For more information on the different indications, please refer Table 2, and information is available in Drugs@FDA: FDA-Approved Drugs and the Postmarket Requirements and Commitments database.[5,6]

DISCUSSION

Within hematology and oncology, CDx assays play an increasing role in securing an optimal therapy for the individual patient, and the FDA considers these types of assays essential for the safe and effective use of a corresponding therapeutic product.[8] The FDA stresses their importance by emphasizing that the use of a CDx assay with a drug must be stipulated in the instructions for use and in the labeling of both the diagnostic device and the corresponding drug, as well as included in the labeling of any generic equivalents of the specific drug. For decades, the FDA has had formal regulatory approval processes in place to ensure that reliable analytical and clinically validated CDx assays are available to support the clinical use of targeted drugs. In this context, an important obligation for the pharmaceutical and biotech companies is to ensure that both drug and diagnostic are developed in parallel to secure simultaneous regulatory approval so that a CDx assay is available at the same time as the drug.

Over the past 5 years, we have experienced several cases where an FDA-approved CDx was not available at the time of the approval of a new targeted drug or a new indication. In these situations, the prescribing information for the drug states that an FDA-approved test for the detection of the specific biomarker is not available. If a clinician wants to prescribe these drugs, the patient selection will need to be performed on the basis of a laboratory-developed test (LDT), if such one is available. The FDA defines LDT as an in vitro diagnostic test that is manufactured and used within a single laboratory.[20] These laboratories are certified under the Clinical Laboratory Improvement Amendments program, which means that the analytical validity must be documented for the assay. However, when it comes to the clinical validity, there are no Clinical Laboratory Improvement Amendments requirements, which means that in most cases the clinical value of the assay is undocumented.[21] Over the years, the FDA and others have reported several problems with LDT assays with respect to quality.[22-24] A recent study conducted to evaluate the performance of LDT next-generation sequencing assays for the selection of targeted therapies conducted across 21 clinical laboratories concluded that the variability in accuracy across these laboratories identified different patient populations.[23] Such a study underlines why it is important for pharmaceutical and biotech companies developing targeted therapies to ensure that an analytical and clinically validated FDA-approved CDx assay is available at the same time as the drug.

When discussing missing FDA-approved CDx assays, it is important to have in mind that most of the drugs mentioned in this article have been approved under the Accelerated Approval Program. This program was instituted to allow for earlier approval of drugs that treat serious conditions and fill an unmet medical need on the basis of a surrogate end point.[25] Drugs and new indications approved on the basis of an accelerated approval will have to fulfill a number of postapproval requirements, and the postmarketing confirmatory trials for the drugs discussed here will also include a CDx assay. In relation to the fulfillment of the postapproval requirements, the FDA has strict rules for reporting on the progress of studies and/or clinical trial activities, as well as the final report submission.[26] Noncompliance with regard to the postapproval requirements may have potentially severe consequences for the pharmaceutical and biotech companies in question.

A review of different publicly accessible FDA databases has shown that at least 10 drugs and new indications have been approved without a CDx assay within the past 5 years. In the respective NDA or BLA Approval Letters, postmarketing commitments are included for the subsequent development of an analytical and clinically validated CDx assay. The first time, the FDA waived the requirements with respect to the simultaneous approval of a CDx assay was in 2017 when pembrolizumab was approved for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors and colorectal cancer. According to the postmarketing commitments, the timetable for regulatory submissions with regard to MSI-H and dMMR CDx assays was December 2019; however, 5 years after the approval of these indications, these assays are still not available. The current review also points to other new drugs/indications with similar problems, so it seems that pharmaceutical and biotech companies are too slow to follow-up on these commitments. CDx assays are of vital importance for the correct use of a number of targeted hematological and oncological drugs; therefore, all parties should take these commitments more seriously.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jan Trøst Jørgensen

Consulting or Advisory Role: Agilent, Alligator Bioscience, argenx, Biovica
Patents, Royalties, Other Intellectual Property: Royalties, Elsevier

No other potential conflicts of interest were reported.

REFERENCES

1. Ross JS, Slodkowska EA, Symmans WF, et al: The HER-2 receptor and breast cancer: Ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 14:320-368, 2009
2. Jørgensen JT, Winther H, Askaa J, et al: A companion diagnostic with significant clinical impact in treatment of breast and gastric cancer. Front Oncol 11:676939, 2021
3. Food and Drug Administration: Table of Pharmacogenomic Biomarkers in Drug Labeling. 2021. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
4. Food and Drug Administration: List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). 2021. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools
5. Food and Drug Administration: Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
6. Food and Drug Administration: Postmarket Requirements and Commitments. https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
7. Food and Drug Administration: Post-approval Studies (PAS) Database. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?sb=msd&s=t&d=U2VhcmNo
8. Food and Drug Administration: Guidance for Industry and Food and Drug Administration Staff. In Vitro Companion Diagnostic Devices. 2014. https://www.fda.gov/media/81309/download
9. Jørgensen JT, Hersom M: Clinical and regulatory aspects of companion diagnostic development in oncology. Clin Pharmacol Ther 103:999-1008, 2018
10. Lara Gongora AB, Carvalho Oliveira LJ, Jardim DL: Impact of the biomarker enrichment strategy in drug development. Expert Rev Mol Diagn 20:611-618, 2020
11. Parker JL, Kuzulugil SS, Pereverzev K, et al: Does biomarker use in oncology improve clinical trial failure risk? A large-scale analysis. Cancer Med 10:1955-1963, 2021
12. Food and Drug Administration: Draft Guidance for Industry and Food and Drug Administration Staff. Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product. FDA, 2016. https://www.fda.gov/media/99030/download
13. Ardini E, Menichincheri M, Banfi P, et al: Entrectinib, a Pan-TRK, ROS1, and ALK inhibitor with activity in multiple molecularly defined cancer indications. Mol Cancer Ther 15:628-639, 2016
14. Food and Drug Administration: Full Prescribing Information for Rozlytrek (Entrectinib) Capsules, for Oral Use. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212725s005lbl.pdf
15. Food and Drug Administration: Approval Letter for NDA 212726 Rozlytrek (Entrectinib). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/212726Orig1s000ltr.pdf
16. Food and Drug Administration: Approval Letter for NDA 212725 Rozlytrek (Entrectinib). 2019. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/212725Orig1s000ltr.pdf
17. Khoja L, Butler MO, Kang SP, et al: Pembrolizumab. J Immunother Cancer 3:36, 2015
18. Food and Drug Administration: Prescribing Full Information for Keytruda (Pembrolizumab) Injection, for Intravenous Use. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s120lbl.pdf
19. Food and Drug Administration: Approval Letter for BLA 125514/S-14 Pembrolizumab (Keytruda). 2017. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125514Orig1s014ltr.pdf

20. Food and Drug Administration: Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories on the Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). 2014. https://www.fda.gov/media/89841/download
21. Robinson SA, Carter AR, Brindley DA: The Changing Regulatory Landscape for Laboratory Developed Tests. The Regulatory Affairs Professionals Society, Regulatory Focus, 2021. https://www.raps.org/RAPS/media/news-images/Feature%20PDF%20Files/21-8_Robinson-et-al.pdf
22. Food and Drug Administration: The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies. 2015. http://wayback.archive-it.org/7993/20171114205911/, https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm472773.htm
23. Pfeifer JD, Loberg R, Lofton-Day C, et al: Reference samples to compare next-generation sequencing test performance for oncology therapeutics and diagnostics. Am J Clin Pathol 157:628-638, 2022
24. Lincoln SE, Hambuch T, Zook JM, et al: One in seven pathogenic variants can be challenging to detect by NGS: An analysis of 450,000 patients with implications for clinical sensitivity and genetic test implementation. Genet Med 23:1673-1680, 2021
25. Food and Drug Administration: Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics Accelerated Approval Program. 2014. https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program
26. Federal Register: Guidance for Industry on Postmarketing Studies and Clinical Trials-Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. https://www.federalregister.gov/documents/2011/04/01/2011-7707/guidance-for-industry-on-postmarketing-studies-and-clinical-trials-implementation-of-section-505o3