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Validation of an electronic program for pathologist training in the interpretation of a complex companion diagnostic immunohistochemical assay☆,☆☆

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Summary Companion diagnostics assay interpretation can select patients with the greatest targeted therapy benefits. We present the results from a prospective study demonstrating that pathologists can effectively learn immunohistochemical assay–interpretation skills from digital image–based electronic training (e-training). In this study, e-training was used to train board-certified pathologists to evaluate non–small cell lung carcinoma for eligibility for treatment with onartuzumab, a MET-inhibiting agent. The training program mimicked the live training that was previously validated in clinical trials for onartuzumab. A digital interface was developed for pathologists to review high-resolution, static images of stained slides. Sixty-four pathologists practicing in the United States enrolled while blinded to the type of training. After training, both groups completed a mandatory final test using glass slides. The results indicated both training modalities to be effective. Overall, 80.6% of e-trainees and 72.7% of live trainees achieved passing scores (at least 85%) on the final test. All study participants reported that their training experience was "good" and that they had received sufficient information to determine the adequacy of case slide staining to score each case. This study established that an e-training program conducted under highly controlled conditions can provide pathologists with the skills necessary to interpret a complex assay and that these skills can be equivalent to those achieved with face-to-face training using conventional microscopy. Programs of this type are scalable for global distribution and offer pathologists the potential for readily accessible and robust training in new companion diagnostic assays linked to novel, targeted, adjuvant therapies for cancer patients.

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1. Introduction

In the 1990s, targeted molecular anticancer therapies constituted only 5% of all drugs approved by the US Food and Drug Administration (FDA). However, by 2013, this figure had climbed to 45% [1]. Many molecularly targeted therapies use companion diagnostic (CDx) assays for patient selection and to support patient safety [2]. Indeed, the FDA reported in 2013 that approximately two-thirds of newly approved agents with breakthrough designations had included a CDx assay [3], highlighting the enduring importance of this strategy. However, the need for accurate interpretation by pathologists of these potentially complex assays is a limitation to the timely introduction of approved therapies.

The recent emergence of whole-slide imaging and advanced software for digital pathology suggests that virtual microscopy might be used for en masse trainings of pathologists to interpret complex assays. The use of virtual microscopy in the professional pathology community, in the form of telepathology, has progressively increased because it streamlines workflows and physician collaborations [4]. Digitized whole-slide images were used in some pathology residency competency evaluations and in certification examinations given by the American Board of Pathology [5]. Computer-based teaching ("e-training") programs increased over the past 2 decades [6], as a number of medical schools [7] and pathology training programs [6,8] have incorporated e-training methodology into their curricula [9-11]. Digital pathology systems were cleared by the FDA for primary diagnostic breast cancer biomarker testing in the United States [12,13]. Advancements in technology for assay interpretation ultimately derive from original interpretation on traditionally stained glass slides.

No study to date has reported on the effectiveness of e-training as compared with traditional, in-person, whole glass slide microscopy in relation to the interpretation of a CDx immunohistochemical (IHC) assay. In this report, we compare the use of simulated virtual microscopy for training practicing pathologists to interpret a CDx IHC assay [14]. This study was conducted in concert with the clinical development program for the MET CDx assay (Ventana Medical Systems Inc, a member of the Roche Group, Tucson, AZ). The antibody (Ab) within the assay binds the MET protein, a transmembrane receptor tyrosine kinase that activates cellular signaling pathways involved in cellular proliferation, motility, migration, and invasion. Amplification of the *MET* gene or overexpression of MET protein is associated with neoplastic transformation and metastasis [15].

In a Roche-sponsored Phase 3 study (Protocol: OAM4971g [17]), the MET CDx assay accurately identified those patients with non–small cell lung carcinoma (NSCLC) who benefited from a MET-targeting therapeutic agent, onartuzumab (Genentech, a member of the Roche Group, San Francisco, CA). Patients with MET+ diagnosis benefited from onartuzumab treatment during the study [16].

The investigative pathologists who diagnosed MET clinical status for the Phase 2 and 3 onartuzumab trials were trained by highly experienced Ventana pathologists with 1.5-day face-to-face workshops. The complexity of this assay, coupled with the ever-increasing incidence of lung cancer, induced a sense of global urgency for pathologist training in the assay.

In this prospective study, we compared the effectiveness of our Digital Learning Platform (DLP) with that of traditional live-training sessions using the MET CDx assay.

2. Materials and methods

2.1. Ethics

Approval to carry out the study was granted by the research ethics board of the study institution, Clarient Diagnostics Services, Inc (Aliso Viejo, CA), in accordance with the Declaration of Helsinki.

2.2. Case slide preparation and staining

The NSCLC cases used in this prospective study were prepared from paraffin blocks containing residual, deidentified, formalin-fixed tissue. Individual serial sections (4-5 μm thick) from each tissue block were mounted on positively charged glass slides and stained with hematoxylin and eosin (H&E), CONFIRM Negative Control Rabbit Ig, and Ventana Anti–Total c-MET (SP44) Rabbit Monoclonal Primary Antibody (Ventana c-MET [SP44] Ab) (Ventana Medical Systems Inc). A BenchMark Ultra automated staining platform with UltraView Universal DAB Detection Kit was used for all cases. Three pathologists experienced in MET CDx assay interpretation provided unanimous interpretations of all reference cases used for training. Accepted classification of clinical scores 0/1+ (negative) and 2+/3+ (positive) were determined for each slide. Ventana MET control slides function as intensity references during evaluation of difficult cases. The slides contained individual pellets of 4 different cell lines that separately exhibited MET IHC staining intensity scores of 0, 1+, 2+, and 3+ when stained with Ventana c-MET (SP44) Ab.

2.3. Ventana MET CDx DLP

The Ventana MET CDx DLP user-operated e-tutorial was developed to simulate in-person clinical training but with interactive digital images. E-trainees were provided a computer with the DLP and were taught how to use the program. They advanced through the modules independently at their own pace, requiring up to 4-5 hours for completion. A screenshot of the DLP interface displayed a single case (Fig. 1). Accompanying each case were thumbnail images located on the right of the screen (Fig. 1A) for each stain in the case. The slide bar at the bottom of the screen would adjust the magnification field