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## Research

# Cy-TEST - A new platform for training and testing in cytopathology

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**Abstract**

**Introduction/ Background:** Clinical training at the European level requires flexible ways to provide education across borders with the goal of a unified way to teach and assess quality. The Cy-TEST project focuses on Cytological Training at European Standard through Telepathology. The project (2014-1-IT01-KA202-002607) has been approved and funded in 2014 by EU within the ERASMUS+ Program. The project consortium is composed of 4 leading university Institutions (COREP and University of Turin, University of Padua, Imperial College of London, IPATIMUP/University of Porto and University of Graz) with technological development and support provided by CRS4. In addition, it benefits from the collaboration of International Organizations (EFCS, Eurocytology, OME) and is open to contributions from additional groups and Societies.

**Aims:** Our aim was the establishment of a platform for the sharing of digital pathology images and of an auxiliary system that will use the latter platform for the distribution of cytologist training courses with an integrated virtual microscopy capability.

**Methods:** The Cy-TEST platform is based on the integration between Moodle, an e-learning platform designed to create personalized learning environments, and OME OMERO, a well-known open source software for visualization, management and analysis of biological microscope images. The former is used to provide access to a database of questions produced by specialized trainers and the latter provides access to digital pathology images and related metadata. We chose to base our infrastructure upon Moodle because it is one of the top leading platforms for online education with a large community of users across both academic and enterprise level, highly customizable and modular. OMERO was chosen because of its compatibility with a large number of image formats for digital pathology images, its handling of image metadata (i.e., TAGs and Regions of Interest) and its easily extensible web platform.

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**Results:** The web platform can be used with a wide range of devices, it is compatible with most of the image formats produced by digital slides scanners and it can scale to a wide student body. Teachers can create courses; populate the Question Bank and aggregate questions in quizzes, while students can take classes and tests. When creating questions, teachers can choose images previously loaded and annotated. We provide two new types of questions: multiple choice, focused on an image and its ROIs, and interactive, where students identify areas on the image by markers that will be automatically compared to instructor's specified ROIs. The currently deployed system holds already a set of several hundreds of images classified by categories (e.g., tissue type and diseases) with associated ROIs identified by pathologists. The Cy-TEST platform provides a full technological solution for a more homogeneous training and testing of cytotechnicians and cytopathologists with uniform quality level assurance mechanism. The system could be easily extended to support the teaching of histopathological diagnosis. Moreover, the Cy-TEST platform paves the way to an e-QUATE test, thus providing an efficient and economical way to replicate the test at European scale (see Branca et al., 2000). The sustainability of the platform and the supported educational material (images, questions and evaluation algorithms) will be guaranteed by its integration in EFCS activities. We expect to distribute the Cy-TEST System for validation by October 2016, for further information contact infocytest@corep.it.

**Keywords:** elearning; telepathology; cytopathology; virtual microscopy.

## Introduction

The use of scanned images distributed and commented via Internet (s.c. Virtual Microscope) is being adopted by several Universities and teaching organizations in order to meet the basic requirement for Medical educational curricula as part of the training in medical and biological courses (see Dee, 2009) and as a tool to improve the quality of morphological diagnostics (Kunze, 2016). The integration within the Learning Management System of teaching institutions of the functionality of a microscope via an interactive application can profitably support the understanding of tissue structure at cellular level, leading to the proper evaluation of biological structures (Kayser et al., 2016). This approach would lead also to other advantages, like the reduced economic costs (the number of microscopes to be acquired is reduced) and the flexibility offered to students by the possibility of choosing time and place for Virtual Microscopy practicing. Moreover, this method can be preferred by students as considered "cooler" than managing a real microscope (see Herrmann et al., 2015 and Ordi et al., 2015).

Essential features needed to realize an effective learning approach are: a user-friendly setting, allowing the analysis of histological and cytological preparation at different magnification; and the possibility of navigating within the images guided by markers and explanatory text pre-inserted by the teachers to point out significant regions (Young, 1994 and Al-Janabi et al.

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2011). Moreover, understanding and learning the process leading to cytological diagnoses can benefit from an algorithmic approach (Zioga and Destouni, 2015).

We have been following these criteria in order to set up a Project, specifically focused on Cytological Training at European Standard through Telepathology. This Project (Cy-TEST Project 2014-1-IT01-KA202-002607), approved and funded in 2014 by EU within the ERASMUS+ Program, is composed of 4 leading university Institutions (COREP and University of Turin, University of Padua, Imperial College of London, IPATIMUP/University of Porto and University of Graz) and the CRS4 (Center for advanced studies, research and development in Sardinia) as technological partner. In addition, the Project benefits from the collaboration of European Organizations (EFCS, Eurocytology, OpenMicroscopy) and is open to contributions from additional groups and Societies.

Previous works realized e-learning platforms to analyze images, organized in categories such as pathologies or anatomical regions, using markers on slides (see Rehatschek, 2011), without a direct interaction by the students (see Sinn, 2013). Our innovative system deeply integrates Virtual Microscopy within the learning system, making the images an active part of the training. In this paper, we describe the open-source e-learning platform we developed for the remote interactive training of cytologists and report on its support for bioimages sharing and integrated virtual microscopy capabilities.

## Methods

The primary features of the e-learning platform we developed are bioimages management and cytologist training courses distribution: this section describes the implementation choices made to realize the infrastructure, illustrated in <Figure 1>, and the criteria followed to choose images and questions that have been included in the system.

### *Bioimages Management System*

The infrastructure component devoted to digital pathology images management is based on:

1. OME OMERO platform, an open source software “for visualization, management and analysis of biological microscope images”;
2. ome-seadragon, the platform specialized viewer we developed.

OMERO (see Allan et al., 2012) has been chosen since it can handle a wide range of bioimages formats, it supports image metadata management and it can be easily extended. OMERO, in fact, is compatible with more than 140 different image formats with an almost complete coverage of the digital pathology ones and natively offers the possibility of storing meta-information, like classification TAGs or Regions of interest (ROI) associated to an image. The access to the images can be both via a Java client (OMERO.insight) and via a web application

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(OMERO.web). OMERO is a de-facto reference system for bio-images management in research with thousands of running installations worldwide.

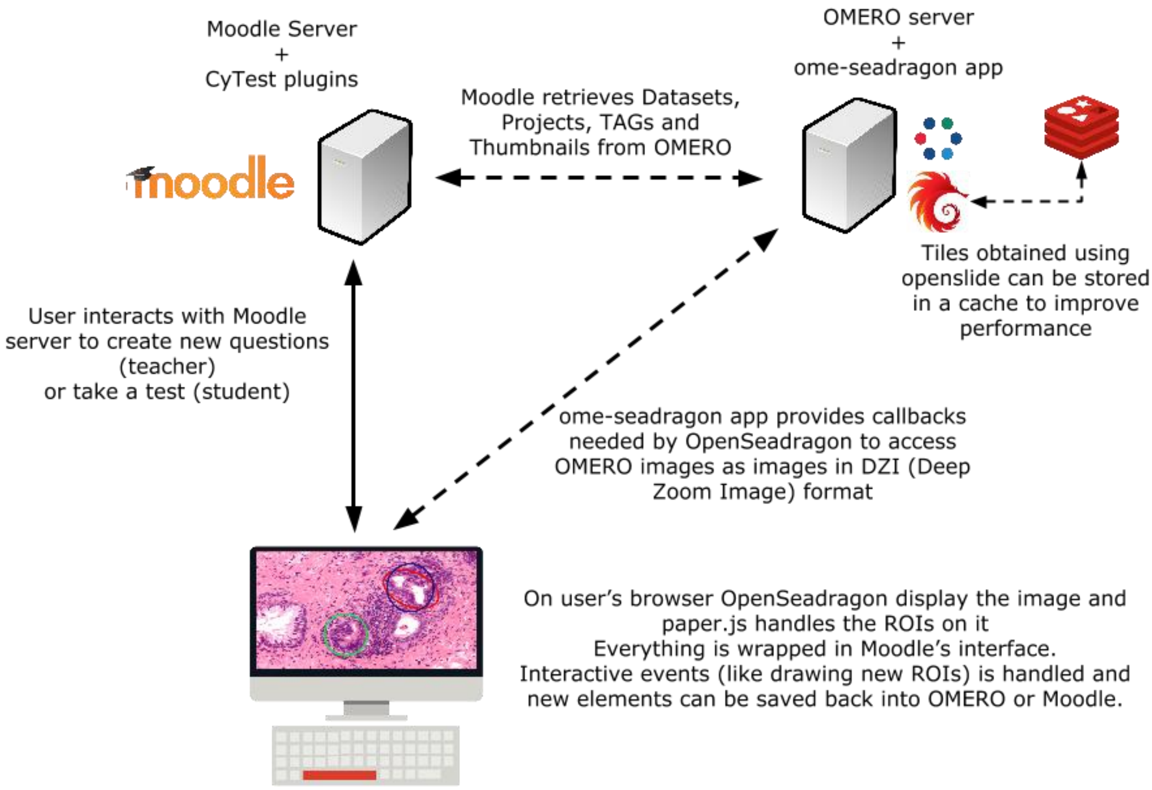


*Figure 1: The e-learning platform architecture.*

To simplify the integration of the images stored within OMERO into an external web system we developed a specialized web application, ome-seadragon. It's based on the OpenSeadragon viewer (version 2.2.1, 2016), an open-source viewer for high resolution images like the ones produced by a digital pathology scanner, and an overlay system developed using paper.js (version 0.9.25, 2015), a Javascript library for vectorial graphic on web, to handle ROIs defined on the image. Our web application acts like a middleware between OMERO.server and our viewer and converts images to DZI (Deep Zoom Image) format, an XML specification defined and maintained by Microsoft (see file format overview in Microsoft's Developer Network website). The conversion process is carried on by different engines that can be configured by the user. Currently, we support rendering based on the openslide library (version 3.4.1, 2015 see also Goode at al., 2013) and on OMERO rendering libraries (which do not support DZI format natively) making ome-seadragon a DZI format wrapper for OMERO. Fast access to the tiles produced by the rendering engine can be optionally provided enabling a cache mechanism, developed using redis (version 3.0, 2016) as backend. The cache mechanism is

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particularly important when dealing with a large amount of users that are watching the same set of images in a relatively short time window (like a class of students taking an examination) because it enables the system to scale without putting the rendering engine under heavy load: once a tile has been rendered the only thing the application must do to serve other requests is access the rendered file and provide it to the other users.

The server-side application of ome-seadragon exports the default RESTful API expected by the OpenSeadragon viewer. New rendering drivers can be added to the system as long as they provide the right callbacks to adhere to the expected API (defined by an interface class). The client-side part of the application is basically a Javascript API that can be used to easily create an instance of the viewer and place over it an overlay where shapes retrieved from OMERO (the ROIs) are drawn using the paper.js library.

Our Javascript API handles the proper conversions needed to adapt a paper.js canvas over the image viewer and bind the two elements in order to handle events propagation (for example, a zoom on the OpenSeadragon viewer will be extended to the paper.js canvas). The client also provides a set of tools that will enable users to actively interact with the image to add new ROIs that can be saved on a third-party system (like a Moodle backend).

### *Training Course Distribution*

The component supporting training course distribution is based on Moodle (Modular Object-Oriented Dynamic Learning Environment) (version 2.9.6, 2016), an open source platform for the creation of personalized learning management system. Moodle is adopted by a vast number of academic institutions and enterprises and provides a set of tools to design training environments that are robust, secure, modular and highly customizable.

We developed a set of Moodle plugins to obtain proper integration with OMERO and to add new types of questions based on images. As an example, some customized modules enable the access to OMERO images as if they were in a standard Moodle repository. Using these components, teachers can navigate OMERO repository by Datasets and Projects and by the TAGs used to classify images, as shown in <Figure 2>.

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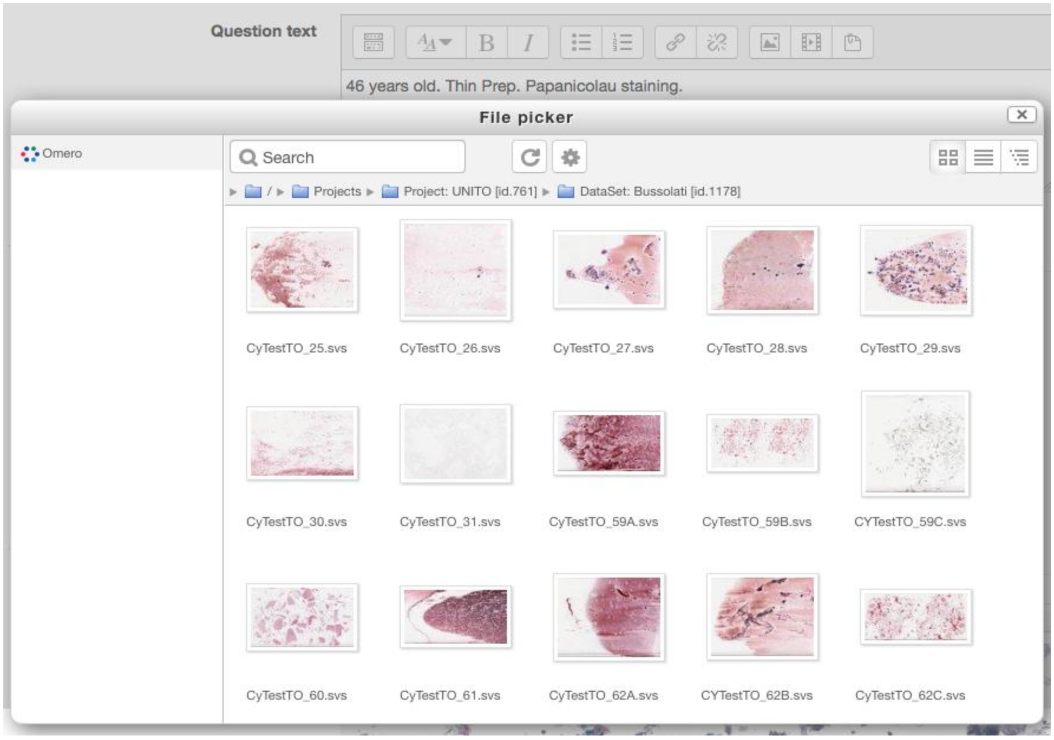


*Figure 2: Navigation in OMERO repository for images selection during question preparation.*

## *Images and questions collections preparation*

The collection of images was strictly related to the aim of the Cy-TEST Project: to present a large variety of cytological patterns, so as to build up a platform to be profitably used for educational programs and quality assessment. Criteria were different for Cervico-vaginal Cytology and extra-vaginal Cytology. The former had to represent the whole array of patterns as classified in the Bethesda system, bound to be presented to Cytologists and cyto-technicians in order to prepare for the QUATE examination. Both, Conventional Smears and liquid based cytology preparations are being presented. A specific area of the system is dedicated to the European quality assessment (QUATE) examination with Mock test and practical session with virtual slides with the aim to accomplish the needed criteria to successfully afford the QUATE test.

Extra-vaginal cytology is instead intended for residents in Pathology. The exercises are arranged in different categories and difficulty levels <Tables 3 and 4>. In order to offer a sufficiently extensive variety of patterns, we planned to collect 1000 images overall, approximately half of cervico-vaginal and half of extra-vaginal Cytology.

Slides are scanned at 40X and uploaded and catalogued in OMERO <Tables 1 and 2>, where they are edited with tagging and annotations by drawing regions of interest (ROIs).

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## Results

The Cy-TEST project is in progress and a number of cases (images) and related exercises have already been uploaded. In April 2016, a total of 447 images and 579 training cases are already present in the system and further 400 images (100 per clinical partner) and from 1 to 5 exercises per loaded image will be available by September 2016. The ensuing step will be the dissemination of exercises and tests to an initially selected group of students, in order to reach a proper feedback of the usability and efficacy of the system. An optimal level of both, sharpness of images and didactic property of questions is required. In order to reach this goal, different levels of assessment are in place:

1. Internal evaluation (made by people in the same contributing institution)
2. 2nd Level Internal Evaluation (made by people in another institution partner of Cy-TEST)
3. External evaluation made by end users and other teachers/experts.

On a more technical level, the result of our work is a web platform for virtual microscopy images – and bioimages in general – distribution and e-learning specialized for cytologists. Our platform is running as a cloud based application on an AWS (Amazon Web Services) virtual host which holds both the images and the courses management systems.

| Manufacturer\Format | Images count |
|---|---|
| Olympus (.vsi) | 33 |
| Leica (.scn) | 162 |
| Aperio (.svs) | 251 |
| Hamamatsu (.ndpi) | 632 |

*Table 1: Images stored within OMERO divided by scanner manufacturer (July 2016).*

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| Tagset | Images count |
|---|---|
| Head and Neck | 17 |
| Breast | 21 |
| Lung | 26 |
| Liver | 29 |
| Effusion | 33 |
| Paediatrics | 54 |
| Lymph Nodes | 112 |
| Gynecological | 152 |
| Thyroid | 158 |
| Pancreas and Biliary | 206 |

*Table 2: TAGs family within OMERO and number of related images (July 2016).*

| Difficulty level | Questions count |
|---|---|
| Simple | 276 |
| Intermediate | 256 |
| Difficult | 112 |

*Table 3: Questions difficulty levels in Moodle and number of related questions (July 2016).*

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| Question category | Questions count |
|---|---|
| Breast | 17 |
| Liver | 25 |
| Effusions | 35 |
| Lung | 36 |
| Thyroid | 49 |
| Pancreas | 51 |
| Paediatrics | 114 |
| Lymph-nodes | 139 |
| Cervico-vaginal Cytology | 216 |

*Table 4: Questions in Moodle grouped by category (July 2016).*

All the software is available as Open Source and the source code can be downloaded from GitHub. The Moodle server provides access to the training system and acts as a gateway to images and meta-information on them (like ROIs and classification TAGs); the OMERO server and the ome-seadragon web application are the components that actually manage and store data related to the images, with the exception of students' answers expressed as ROIs which are handled by Moodle.

Using the system, teachers can use previously loaded images and ROIs (defined by themselves or by other users of the system) to create new questions that can populate customized courses and that can be aggregated in quizzes to enrich the Question Bank; students can take classes and tests.

As shown on the tables above, questions are categorized by difficulty level or by topic.

The current version of the system supports two different types of questions:

1. Questions with answer based on images <Figure 3>: images are displayed only as a reference for the question. Teacher must only choose which image and, optionally, ROIs will be displayed; students could have controls to navigate the image (if teacher decides to enable this kind of control);

2. Questions with answers given interactively on images <Figure 4>: answers must be given as markers on the images. Teacher must choose an image and a set of

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related ROIs; the ROIs are then divided in two groups: those that can be displayed as a guide for the student -- if considered useful by the teacher, and those that identify regions of the image that are considered by the teacher as good, possible answers; students will only see the "guide type" ROIs. Students can drop one or more markers (the teacher can set this limit) on the image and the Moodle plugin will calculate the score based on the position of the markers with respect to the ROIs selected by the teacher. If more than one marker hits the same answer, only one of them will be considered as a good answer.

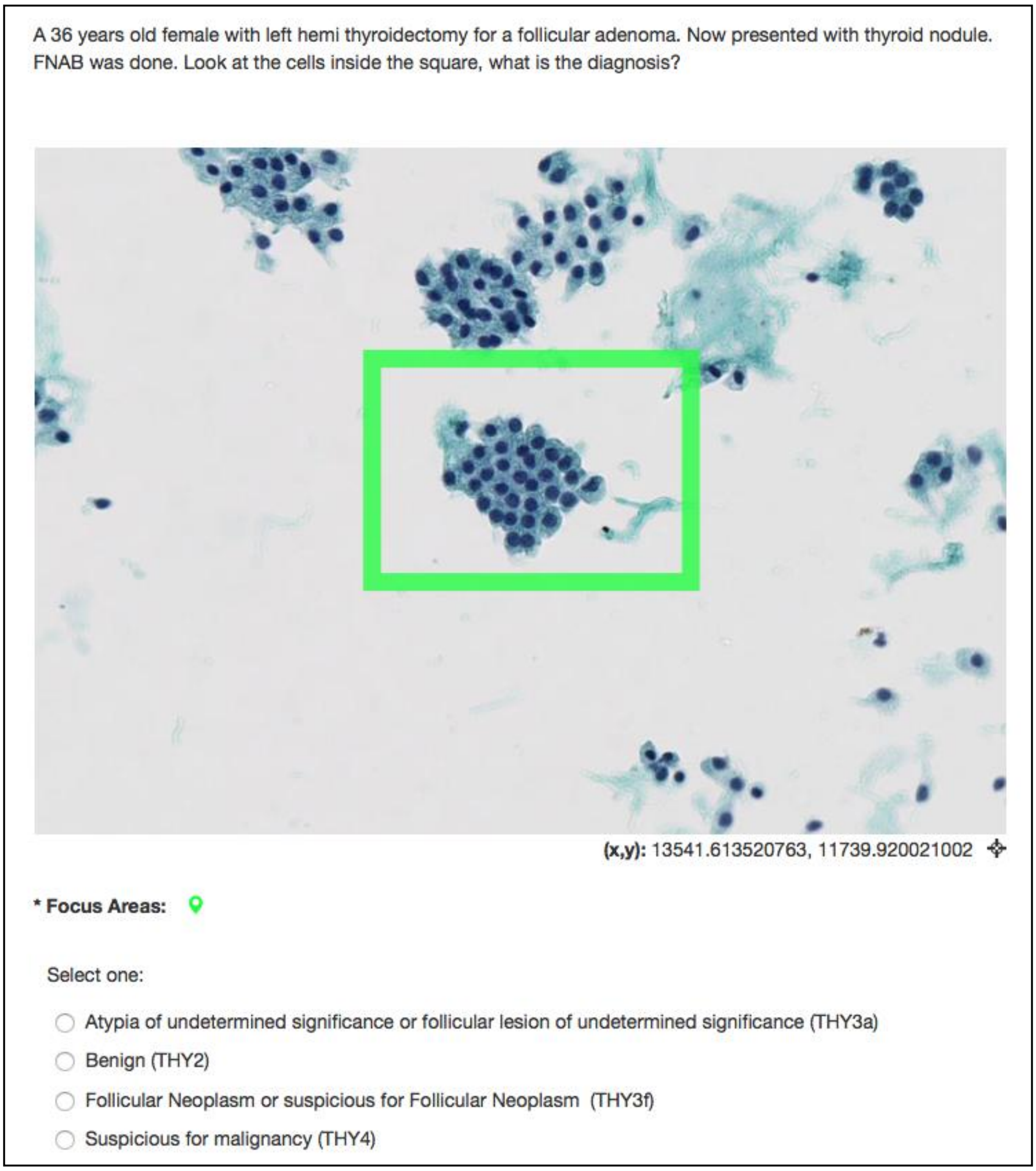


*Figure 3: Multiple choice question example.*

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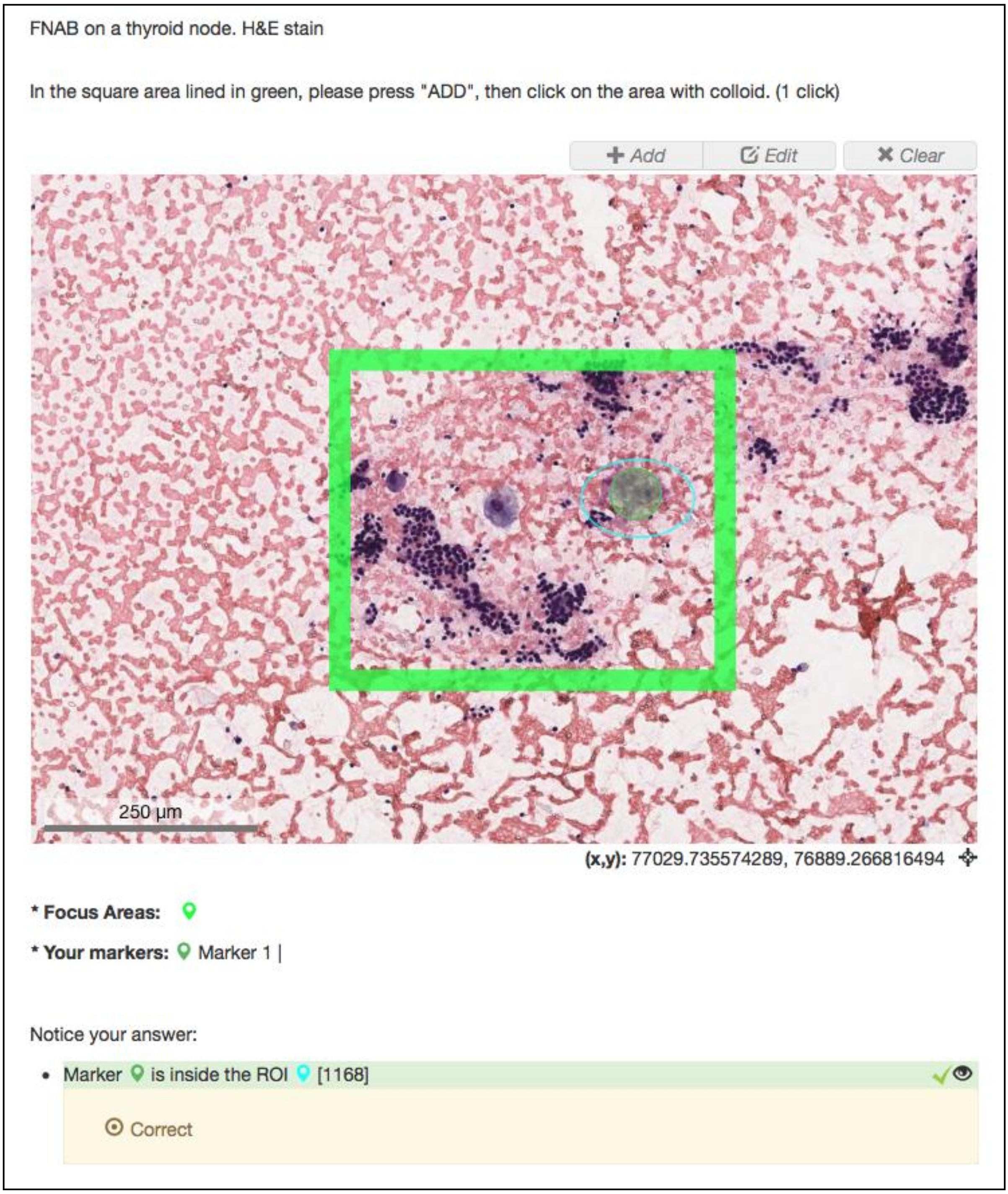


*Figure 4: Interactive question example: in the first image the student answers the question adding a marker in the focus area inside the rectangle; in the second image the correct answer is displayed as a feedback for the student.*

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Another useful feature provided by the system is the possibility to use one or more images and related ROIs as feedback for the answers <Figure 5> so that the student can be guided to further study material.

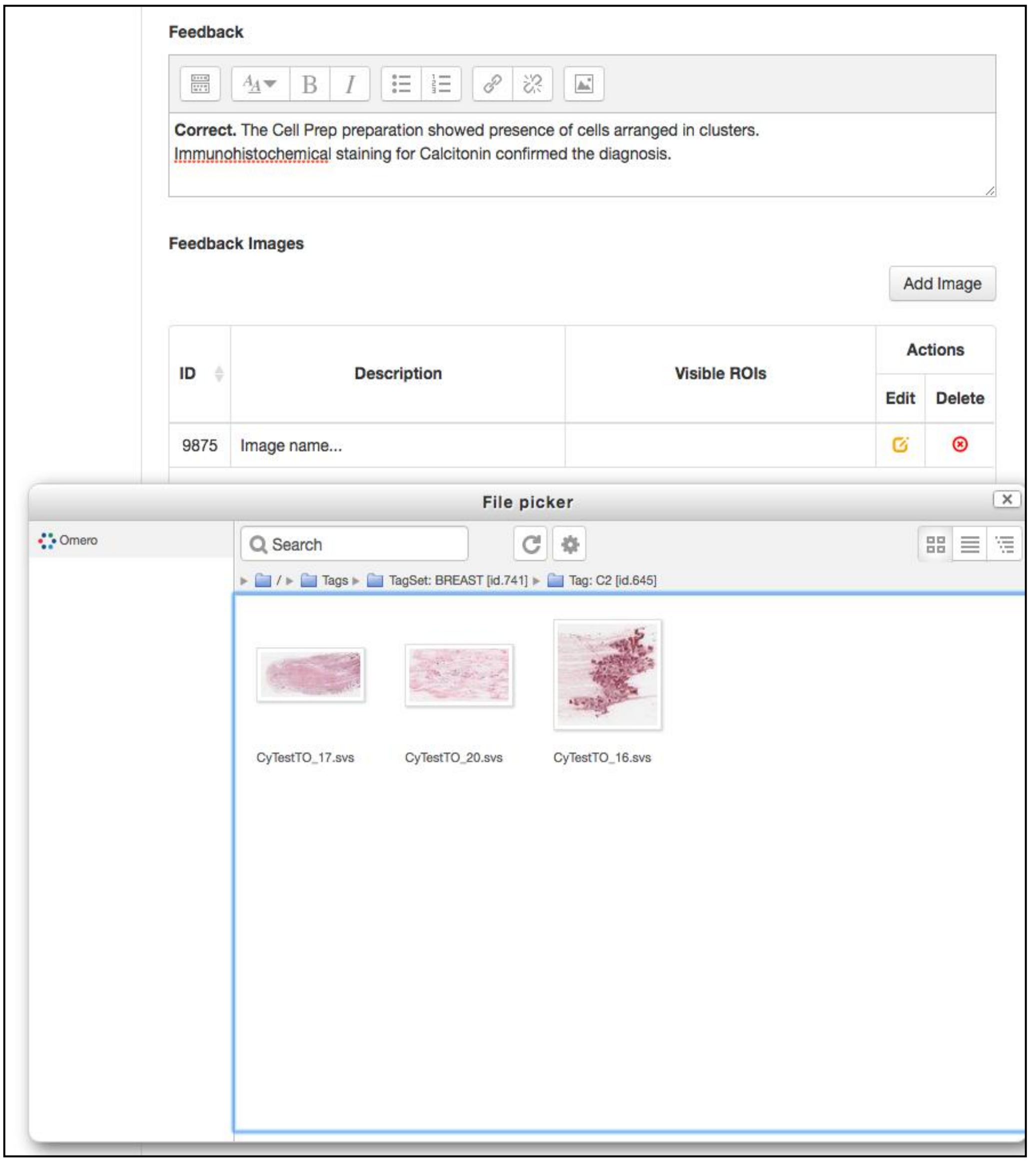


*Figure 5: Images and ROIs can be included in the feedback of a question.*

## Conclusions

The Cy-TEST platform is intended to both improve the educational level in Cytology and assess the quality level of diagnostic abilities. It is paving the way to a more homogeneous training

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and testing of cytotechnicians and cytopathologists. The technological approach chosen is flexible and might lead to the development of a similar system for histopathological diagnosis to be offered to pathologists in training and consultant histopathologists. The innovative approach adopted here allows a sophisticated interaction between students and digital pathology images, an important step propaedeutic to the final development of an electronic version of the QUATE test (e-QUATE), thus reaching a popular, inexpensive and efficient impact.
The system, which will be an integral part of EFCS activities so as to guarantee its sustainability, represents a move towards a technically-based improvement of quality level assurance, which is what patients request.

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