

Utilizing virtual microscopy for quality control review

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1. Introduction

Virtual Microscopy (VM), the technique of digitizing microscope slides with common objective magnifications, may be equivalent to original glass slides on microscopes and will provide diagnostic image quality. Based on this technology an automated pathology review system can be designed in order to facilitate a more efficient quality assurance (QA)/quality control (QC) review process. The Gynecologic Oncology Group Tissue Bank (GOGTB) is funded by the National Cancer Institute (NCI) and located at Columbus Children's Research Institute in Columbus, OH. The complexity of the GOGTB operation requires a reliable QC program that is accessible to multiple out of site/out of state reviewers on a regular basis, ideally 24 hours a day, 7 days a week. In this setting, VM offers a reliable and potentially cost efficient alternative to the more classical method of glass slide peer review process that involves time consuming and costly packaging and mailing of material.

The Virtual Microscopy Pilot EndeavoR (VIPER) (Fig. 1) pilot project automates the QC review process by allowing expert reviewers to remotely view digital images via the Internet. The VIPER system notifies reviewers of new cases and allows reviewers to identify significant slides, complete cases, request accounts, and reset accounts automatically. VIPER also streamlines

the process utilized by the GOGTB by assigning user accounts, passwords, cases, and slides electronically and allows the GOGTB to administer review protocols by the cooperative group and/or submitting institutions. The VIPER system was designed and developed after a thorough analysis of the GOGTB workflow (Fig. 2).

Prior to implementing VM, the QC process required that glass slides and paper forms be physically shipped between the GOGTB and the reviewing pathologists resulting in extended QC review times and substantial shipping costs. VIPER facilitates translational research in gynecological cancer by providing a web-based pathology review and a digital archive of original pathology material.

2. Pathology utilization

Pathologists have traditionally utilized microscopes to aid in the diagnosis and treatment of disease, but modern image capture technology has provided new methods to review specimens. Virtual Microscopy is the technique of digitizing a glass slide with commonly used objective magnifications producing a digital virtual microscope slide that can be viewed with a personal computer. A VM slide is the equivalent of the original glass slide on a microscope. It provides diagnostic digital images (DI) of good quality, allowing users to navigate and view the image at multiple magnifications and at any time.

There are numerous benefits associated with the use of DI. Any tissue stained and prepared on a traditional glass slide setting can be scanned. Staining methods are variable, and include histochemical and immunohistochemical stains. The tissue is available for rapid

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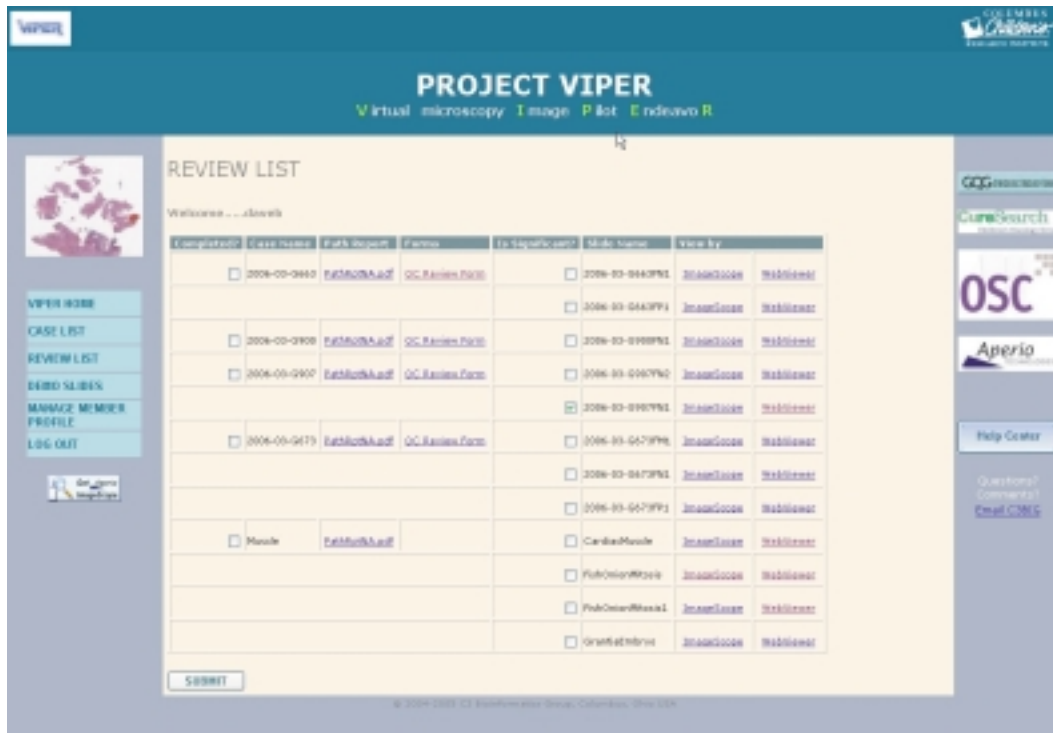


Fig. 1.

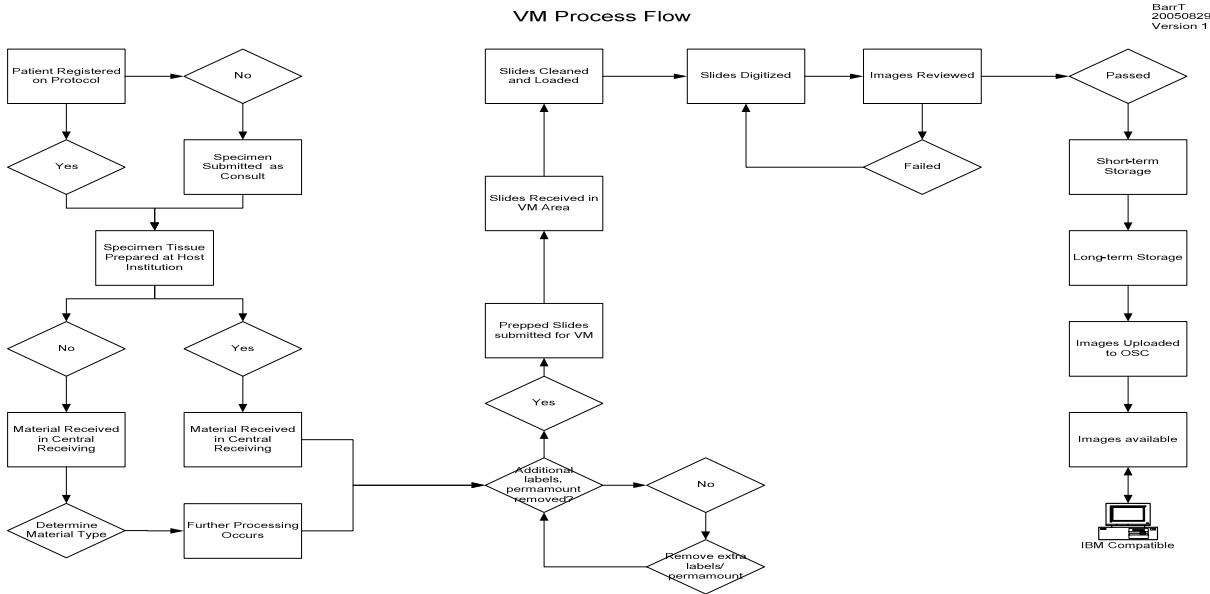


Fig. 2.

review once the electronic image from a master slide is created. This eliminates the need to ship glass slides to multiple reviewers, and allows for images to be reviewed simultaneously by multiple reviewers. This format is extremely helpful when diagnostically difficult cases or unique tissue findings (likely confined to a single tissue slide) are reviewed. Using VM reduces the number of broken slides and lowers (or can even eliminate) shipping costs. Digital annotations can be performed on the images with no impact on the original glass slide. DI creates a retrievable database of submitted material that can be used for confirmation of eligibility criteria, creating a digital archive that documents the original pathology material and quantifies the pathology images. The use of VM enhances the selection of research material, providing an on-line review of original material prior to an investigator selecting or requesting tissue. DI can also be used to educate medical and research professionals involved in research and/or diagnostic tissue-based projects and as part of a quality control/quality assurance program. The objective of the GOGTB is to fully-utilize this technology by implementing an automated pathology review system to facilitate a more efficient and cost-effective QC review process.

3. VM technology

Although several companies currently offer imaging products designed for use on glass slides we will focus

on the systems currently used by the GOGTB. After negotiating with several vendors, the GOGTB selected Aperio Technologies as the initial vendor for all digital imaging of tissue specimens. Much of the decision process was related to the line scanning technology and the rapid scan times provided by the Aperio system. According to Aperio Technologies, "Line scanning is a significant advancement in rapid, high resolution virtual microscopy. Line scanning is a superior methodology to image tiling. ScanScope® scanners do not use a fixed-area camera to capture thousands of individual image tiles but instead employ linear-array detectors in conjunction with specialized motion control components, a microscope objective lens and customized optics."

A variety of tools are required to successfully implement VM. These tools consist of both hardware and software. The GOGTB currently utilizes both vendor-supported and custom-developed software as well as the ScanScope® T2 patented linear-array slide scanner to fully deploy virtual microscopy into the GOGTB business processes.

The main hardware element is the ScanScope® T2, a patented linear-array slide scanner, which is utilized with a 120-slide autoloader to provide the digitization of entire microscope slides at high resolutions. These images are then compressed and stored for later retrieval. The use of a Virtual Slide Repository (VSR), a high-end computer that runs all ScanScope® software applications, provides temporary local storage of all

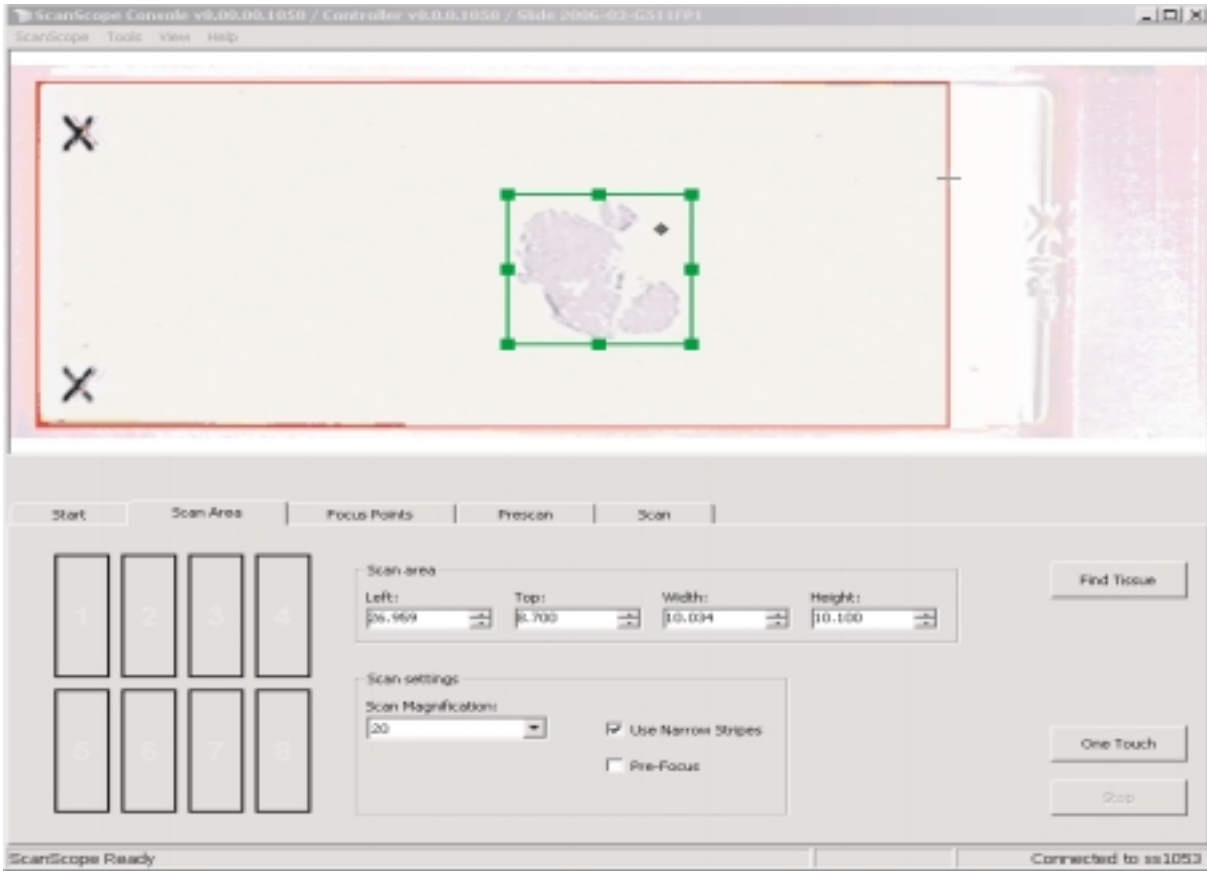


Fig. 3.

virtual slides created with the ScanScope®. Images that are temporarily stored on the VSR are then securely transported via the SSH Secure Shell application to the Ohio Supercomputer Center (OSC). The OSC currently provides 10 terabytes of storage space in a secure Linux environment for storing and serving digital images.

There are multiple software components that are utilized with the T2 system. The first is the ScanScope Console (Fig. 3), provided by Aperio Technologies, that provides the user with an interface to the slide scanner. ScanScope Console allows the user to customize the scanner setup to satisfy a particular user's needs. This customization includes several routine options such as the selection of the desired slide magnification, the number of focus points, and the area of the slide to be scanned. The Console also allows the user to configure more specialized features by providing users with the ability to dictate data file formats, compression amounts as well as create custom parameter sets for specific tissue types.

Spectrum Information Manager (Fig. 4) is another tool provided by Aperio Technologies to assist users with integrating digital imaging into current business processes. The application accesses a database that houses vendor-provided fields and gives the user the ability to store and organize custom fields. Spectrum integrates with the ImageScope™ allowing the user to view digital images and perform image analysis on these images. Spectrum allows users to edit slide data as well as manage slide images by sorting, filtering, searching, and removing data and images. All data collected and stored in the Spectrum database can be extracted.

Virtual Slide Manager is software which is used with the VSR for tracking slide data and managing the workflow associated with the virtual slides. All slide data is maintained and updated in a database table which provides specific information about each slide including assay information as well as customizable fields.

A very important software component of the overall system is the ability for users to view the actual



Fig. 4.

slide image. As images are available for review at the OSC, the reviewers need a software viewer to view, pan and zoom the digital images. Current reviewers at the GOGTB utilize either the Apero WebViewer (Fig. 5) or Apero ImageScope™ (Fig. 6) software to view digital images. Although both the WebViewer and ImageScope™ viewers provide diagnostic quality images additional functionality is provided by the ImageScope™ application.

The Apero WebViewer allows the viewing of images that are displayed on a web page and can be remotely accessed by most web browsers. Use of WebViewer does not require a download or plug-in and is primarily used by Macintosh users. Apero ImageScope™, a client-side software package, is available only to users

with Microsoft Windows 2000 or Microsoft Windows XP for viewing virtual slides. ImageScope™ provides additional functionality over WebViewer which includes authoring annotations, integrated image analysis, digital slide conferencing, more convenient navigation options, and faster rendering of images. The Digital Slide Conferencing (DSC), provided by Apero Technologies, promotes collaboration by enabling multiple reviewers to simultaneously and synchronously view an image with ImageScope™ and an internet connection.

Currently the GOGTB uses the Digital Slide Studio (<http://www.aperio.com>) to compress raw data provided by the scanner to make the file sizes more manageable. File sizes vary by tissue size and desired magnifi-

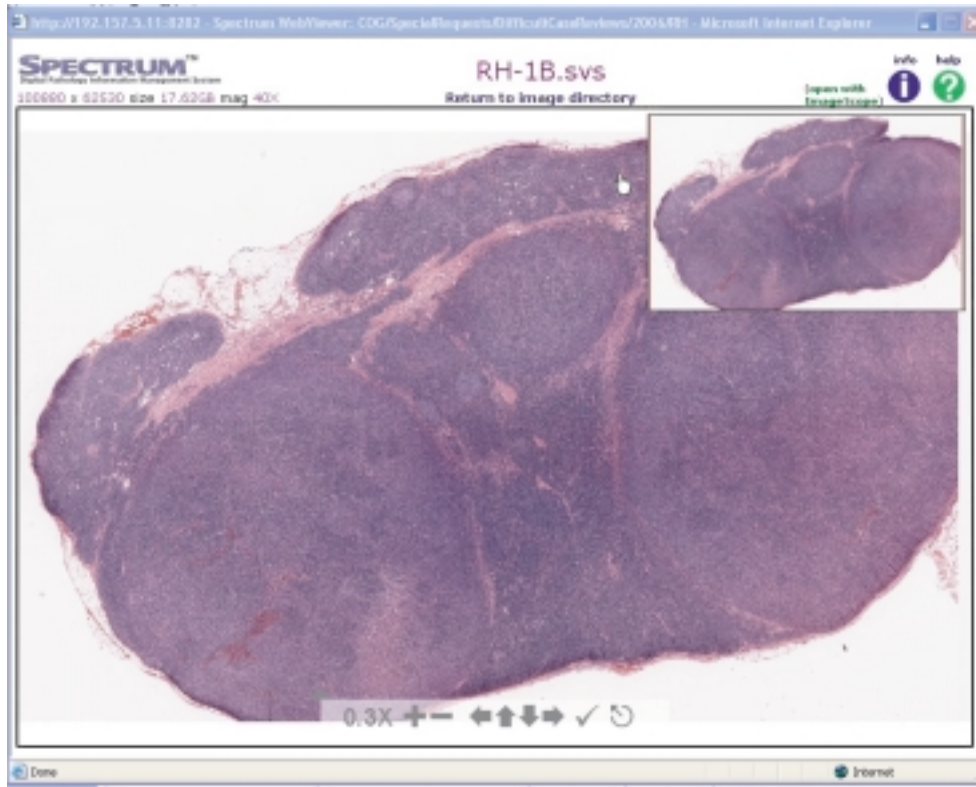


Fig. 5.

cation; image data generated by linear-array slide scanners is generally large and requires data compression to reduce the file sizes prior to making that data available to reviewers. As the popularity of computer aided diagnosis (CAD) has increased, issues related to image compressions has become much more challenging.

In an effort to facilitate the use of tissue microarrays with VM the GOGTB utilizes TMA LabTM (Fig. 7) which is a software component provided by Aperio Technologies. TMA LabTM provides a graphical user interface to assist users in locating and identify spots within a Tissue MicroArray. TMA LabTM also allows users to open multiple spots simultaneously, pan and zoom spots, and compare stain intensity of the spots. A composite TMA can also be created by allowing users to select spots from multiple Tissue MicroArrays. The TMA Lab software is increasing in its use due to the limited availability of consented human tissues. Tissue microarrays are now becoming more popular to maximize use of these valuable tissues. Finally the TMA LabTM provides the user with the ability to both import and export research data in a variety of formats.

The complete VM process also utilizes customized software developed by the GOGTB informatics group

to meet the workflow of the operations staff and the reviewers. Due to the complexity and variety of slide names encountered at the GOGTB it became necessary to create a simple application to interface with data files exported from the Workflow Manager application. This renaming software reads the exported Comma Separated Value (CSV) file and renames all files located in local storage to the preferred slide names and moves these files to the designated location.

At the GOGTB all specimens must be reviewed by expert pathologists prior to these specimens being made available to researchers. Historically this process has required that glass slides, pathology reports, and papers be physically shipped to expert review pathologists to verify diagnoses provided at the patients local institution. The Virtual Microscopy Pilot Endeavor (VIPER), an automated digital pathology review system, is a custom built application designed to replace the historical review process.

The VIPER pilot project is designed to automate the pathology QC review process by allowing expert pathology reviewers to remotely view digital images via the Internet. The VIPER system allows the reviewers to identify significant slides (i.e. those slides

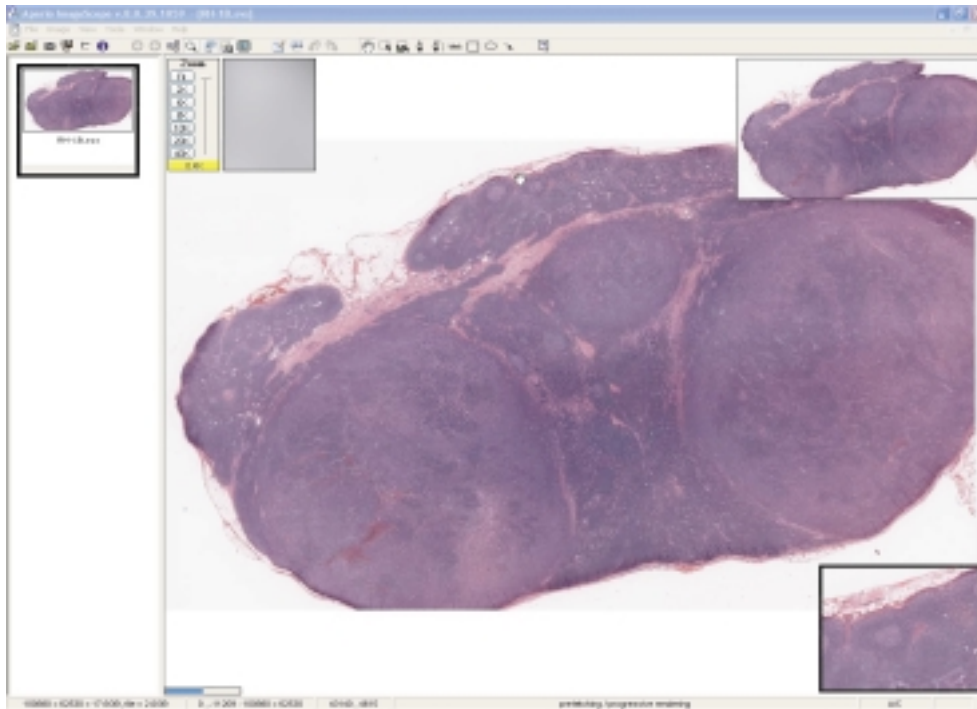


Fig. 6.

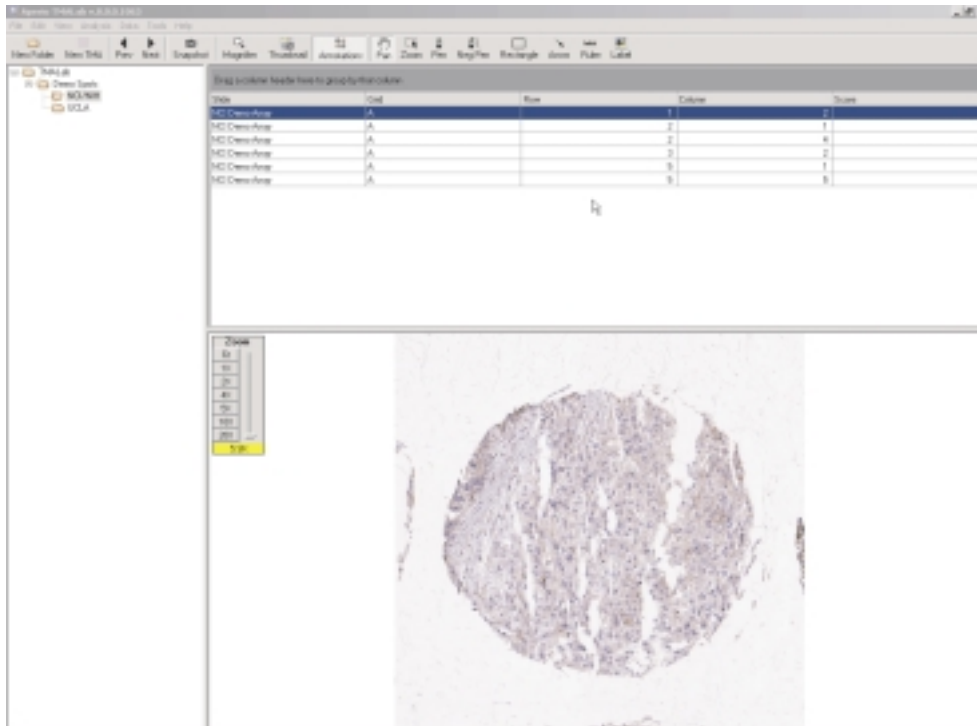


Fig. 7.

imperative to making diagnosis and quality decisions), complete case review, request accounts, and reset accounts automatically. VIPER was custom-designed to allow GOG TB operations staff to not only assign user accounts, passwords, cases, and slides, but also to administer review protocols, per cooperative group, and per institution. VIPER was developed by the GOGTB Informatics Group utilizing various Linux-based technologies including Apache Tomcat, Hypertext Markup Language, JavaScript, JavaServer Pages, and MySQL.

To implement the VM technology, it was imperative to objectively review the benefits and caveats of the VM, validate the technology, and implement VM into to current staff workflow. VM facilitates translational research in gynecological cancer by providing both a web-based pathology review and a digital archive of original pathology material submitted for confirmation of eligibility criteria in a retrievable database. By utilizing VM, the technique of digitizing microscope slides, the GOGTB is able to provide expert review pathologists with digital images used for diagnostic quality assurance. Building on previous experiences VIPER

further automates the pathology review process by allowing reviewers to securely review and identify clinically significant slides, complete cases, request accounts, and reset accounts automatically. The system also notifies the review pathologists by electronic mail of new cases.

4. Conclusion

VM will facilitate translational research in gynecological cancer by providing both a web-based pathology review and a digital archive of original pathology material submitted for confirmation of eligibility criteria in a retrievable database.

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Aperio Technologies.



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