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The Virtual Microscopy Database—Sharing Digital Microscope Images for Research and Education

Lisa M. J. Lee,[1] **Haviva M. Goldman**,[2] **Michael Hortsch**[3,4*]
[1]Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, Colorado
[2]Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, Pennsylvania
[3]Department of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, Michigan
[4]Department of Learning Health Sciences, University of Michigan Medical School, Ann Arbor, Michigan

Over the last 20 years, virtual microscopy has become the predominant modus of teaching the structural organization of cells, tissues, and organs, replacing the use of optical microscopes and glass slides in a traditional histology or pathology laboratory setting. Although virtual microscopy image files can easily be duplicated, creating them requires not only quality histological glass slides but also an expensive whole slide microscopic scanner and massive data storage devices. These resources are not available to all educators and researchers, especially at new institutions in developing countries. This leaves many schools without access to virtual microscopy resources. The Virtual Microscopy Database (VMD) is a new resource established to address this problem. It is a virtual image file-sharing website that allows researchers and educators easy access to a large repository of virtual histology and pathology image files. With the support from the American Association of Anatomists (Bethesda, MD) and MBF Bioscience Inc. (Williston, VT), registration and use of the VMD are currently free of charge. However, the VMD site is restricted to faculty and staff of research and educational institutions. Virtual Microscopy Database users can upload their own collection of virtual slide files, as well as view and download image files for their own non-profit educational and research purposes that have been deposited by other VMD clients. Anat Sci Educ 11: 510–515. © 2018 American Association of Anatomists.

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INTRODUCTION

For about 350 years, microscopy has been the principal approach for the structural analysis of living organisms at the cellular level. Technological advances in microscopy have not only promoted the work of researchers in uncovering the structure–function relationship of cells, tissues, and organs but also have left their mark on the teaching of several biological and medical disciplines, specifically histology, pathology, and more recently cell biology.

Histology and pathology, the study of tissues and cellular diseases, are visually oriented subjects which require learners to acquire the mastery of analyzing and interpreting microscopic images of cells, tissues, and organs (Hamilton et al., 2009; Helle et al., 2010). Since the end of the 19th century, that skill has primarily been taught to medical and dental students using optical microscopes in combination with glass slide sets containing stained tissue sections (Bloodgood, 2005). However, the high cost of good-quality light microscopes, tissue slide sets, and the maintenance and replacement of these resources, as well as the limited availability and variability of certain tissue specimens pose significant barriers to the use of traditional light microscopy for histology and pathology education at many new institutions, especially in the developing world.

When virtual microscopy was introduced about 20 years ago, it soon provided a popular alternative to classical light microscopy and is now progressively replacing the traditional

*Correspondence to: Dr. Michael Hortsch; Department of Cell and Developmental Biology, University of Michigan Medical School, 109 Zina Pitcher Place, Ann Arbor, MI 48109. E-mail: hortsch@umich.edu

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laboratory-based method of teaching histology and pathology (Gu and Ogilvie, 2005; Bloodgood and Ogilvie, 2006; Coleman, 2009; Dee, 2009; Drake et al., 2009; Hortsch, 2013). Digital tissue image files are typically produced from traditional histology/pathology glass slides by using a whole slide scanner, a light microscope with an automated stage, and a high-resolution digital camera (Glatz-Krieger et al., 2003a; Gu and Ogilvie, 2005). Special software tiles the individual image fields together to generate a complete composite image of the tissue specimen at high resolution. Similar to Google Earth (Google Inc., Mountain View, CA), just at the microscopic scale, these large electronic image files (sometimes exceeding several gigabits in size) are stored on a central computer server and can be retrieved via the Internet or a local network. Using one of a number of digital viewer applications or an Internet browser, students can display these images on their computer screen. As only a small part of the entire digital image file is downloaded for a field of view, students can quickly pan across the image and zoom in or out to get an overview of the entire slide or search for smaller details at higher magnification. Learners usually respond positively to the introduction of virtual microscopy and several publications have reported a corresponding improvement in learning outcomes for students enrolled in histology or pathology courses (Goldberg and Dintzis, 2007; Husmann et al., 2009; Wilson et al., 2016).

Virtual microscopy has many advantages for teaching histology and pathology, including the relatively low cost of maintenance, reduced economic burden related to the physical laboratory space and time, and increased accessibility to the learning material (Heidger et al., 2002; Krippendorf and Lough, 2005; Patel et al., 2006). In contrast to providing sets of glass slides of variable quality to every student, all students have equal access to the same collection of high-quality images. Virtual slides provide an unprecedented flexibility to the study of histology and pathology—allowing users to view slides almost anytime/anywhere, to produce annotations for enhancing student learning, and to integrate slides into other digital resources. Considering all these advantages, combined with the ubiquity of Internet access, it is no surprise that many new educational institutions are adopting virtual microscopy in lieu of a traditional histology and pathology laboratory approach. Even established universities are increasingly adopting virtual microscopy, often switching to using virtual microscopy exclusively (Drake et al., 2009, 2014).

Despite these well-documented advantages of virtual microscopy, it is important to highlight some limitations of this technology. Virtual microscopy is innately dependent on the proper functionalities of computer hardware, software, data storage units, networks, servers, and an ongoing maintenance of all these pieces, which come at a variable cost. Thus, due to limitation of their local network systems or restricted Internet access, adopting virtual microscopy may not be cost-effective or even attainable for some users. In addition, virtual microscopy still has several other shortcomings for educational and clinical use. One is the lack of expert or peer support when students view virtual microscopy images on their own. This has been identified as a barrier to student learning (Yen et al., 2014). The advent of enhanced features in virtual microscopy platforms such as annotations and quizzes (Rosenthal and Lee, 2015; Lee and Rosenthal, 2017) hold promise in reducing this barrier. Other disadvantages of virtual microscopy include a reduced variety of available images and the lack of depth perception that are available using optical microscopy. Due to slide scanning cost and time restrictions, most virtual image collections consist of only exemplary slides with optimal tissue architecture that are derived from a much larger glass slide pool that encompasses normal tissue diversity. The three-dimensionality of tissues is innately difficult to teach due to the use of thin microtome sections. In optical microscopy, the ability to *z*-scan (focus at different depth of the thin tissue section) makes an understanding of the three-dimensionality of tissues and organs more practical. This is currently not possible with most virtual microscopy systems, as they scan slides at only one plane of focus. Whole slide scanners and image viewers that perform multiplane focal scans and allow virtual image users access to the *z*-plane are still new and too expensive for widespread use at this time. Lastly, the ability to use and operate optical microscopes is still considered an important competency by many educators, researchers and clinicians (Pratt, 2009; Hortsch, 2013). Thus, the exclusive use of virtual microscopy for education may disadvantage those students who will be required to operate optical microscopes during their research and clinical duties. With time, these inadequacies of virtual microscopy may be overcome by advances in technology and by virtual microscopy equipment and software becoming more robust, ubiquitous, and inexpensive.

The production of high-quality virtual microscopy image files has two essential requirements (Glatz-Krieger et al., 2003a). First is a minimum of at least one exemplary glass tissue slide for each educational object (tissues and organs), prepared with sufficient quality to preserve unique histological features. The second requirement is a whole slide imaging system, with a price tag between US $100,000 and $200,000. For many teaching or research institutions, this expense constitutes a major roadblock for the creation of their own virtual microscopy collection. Institutions fortunate to have access to such an imaging system have generated their own virtual microscopy image collections and have shared these collections with colleagues or other institutions on an individual basis. Such sharing of virtual microscopy images has the benefit of increasing the diversity of image material and a variety of available histological staining and imaging techniques. Until recently, however, there was no mechanism for educators and researchers to access, distribute, and share a repository of virtual microscopy image files on a global scale. This article describes a solution to this problem, the Virtual Microscopy Database (VMD), which is designed to pool resources and to promote the sharing of virtual microscopy image files by users for educational or research applications.

DESCRIPTION

The VMD arose as the brainchild of the authors and a community of histology educators informally organized in the Digital Histology Interest Group (DHIG) of the American Association of Anatomists (AAA) (Bethesda, MD). Combined, the authors and DHIG members have many years of experience using a virtual microscopy approach for histology and pathology education. It was noted by the DHIG community that there is a great demand for virtual microscopy images from both national and international educational institutions. The lack of diversity in any single institutional collection of digital histology slides was also an important concern. Especially educational institutions in the developing

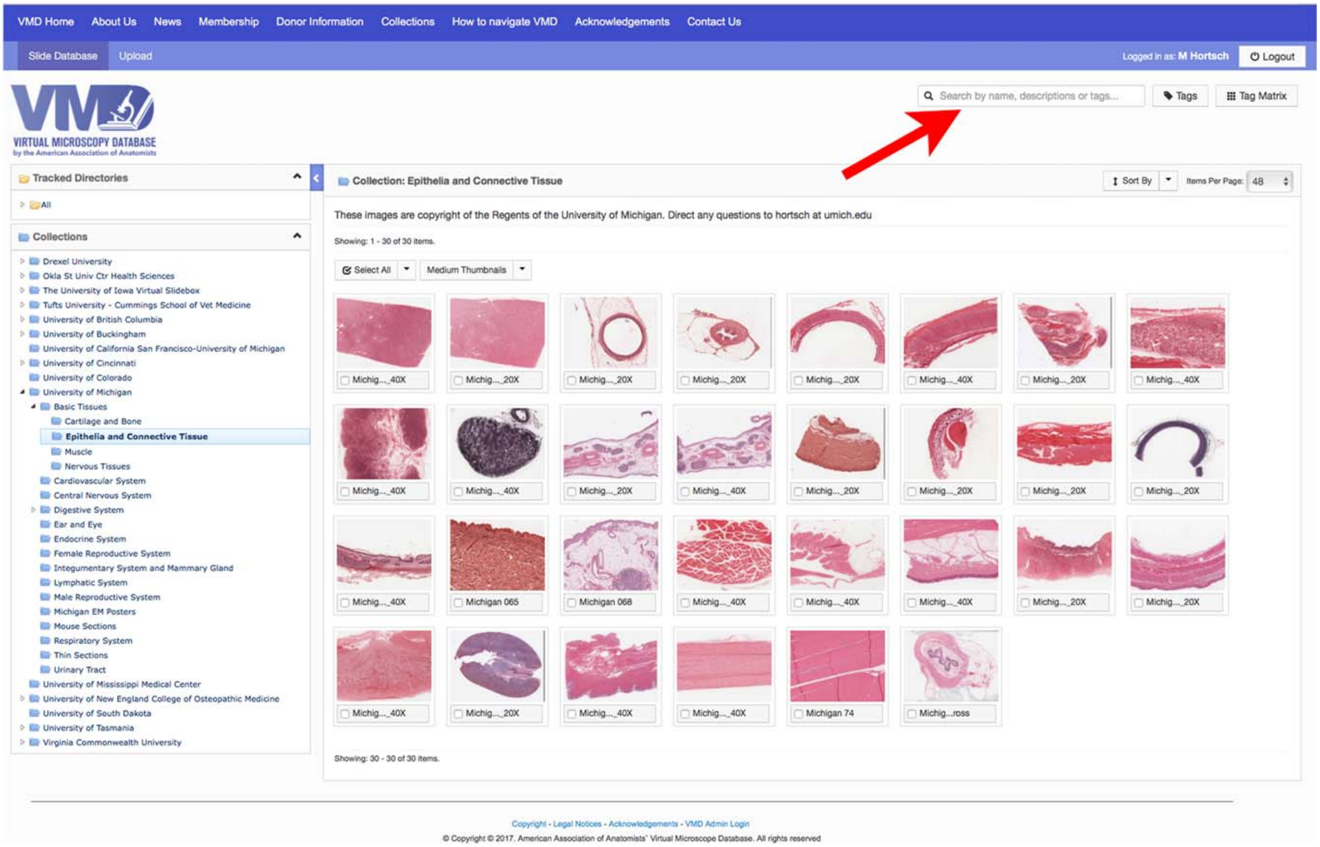

Figure 1.

The VMD content is currently organized in 15 institutional collections that were generous provided by individuals from these universities. Users can find virtual slides of interests by browsing each institutional folder and its subfolders, by perusing thumbprints of the images in each folder, or by using the database search engine (red arrow).

world needed help for transitioning from traditional optical microscope laboratories to more cost-efficient and flexible virtual microscopy technology. However, an efficient modality for sharing virtual microcopy files had been lacking at that point, which called for a global and comprehensive solution.

A grant award from the AAA Innovations Program by the American Association of Anatomists funded the creation of a virtual microscopy file-sharing platform—the Virtual Microscopy Database (VMD). The VMD webpage was designed as an intuitive user interface for signup, login, access to the VMD content, and for uploading and downloading desired virtual microscopy image files. The VMD website was also seamlessly integrated with the database management and virtual slide viewer software, donated by MBF Bioscience Inc., (Williston, VT). The website and database was launched in April 2017 (VMD, 2018).

The viewing and downloading of virtual image files require a one-time registration which allows the subsequent free use of the database. As the primary mission of the VMD is to provide a global resource sharing platform, rather than providing an educational or course management application, only educators and researchers from established educational and scientific institutions, non-profit foundations and museums are able to register and access the VMD content. In addition, current technical limitations will not support hundreds or thousands of students accessing the VMD site simultaneously, making it necessary to restrict user access to the VMD.

A number of free Internet websites with virtual histological and pathological images exist (Glatz-Krieger et al., 2003b; Lundin et al., 2004; Teodorovic et al., 2006; Lundin et al., 2009; Roßner et al., 2011; Sander and Golas, 2013). However, these websites usually serve local needs and do not always support other curricular requirements. In addition, most of these websites are based on only a single institutional image collection which might lack a diversity of microscopic imaging technologies, histological stains, and normal specimen variations. In addition, several of these projects only have a limited number of specimens addressing a specific pathological topic. None of these reported databases allows for the downloading of the virtual image file, thus limiting their use for educational purposes. In contrast, the VMD permits educators to download the image file and to adapt the material to their and their students' needs and the local course structure.

Currently, the VMD site offers over 2,600 virtual microscopy files donated by educators and researchers from 15 different universities (Fig. 1). These image files are predominantly in the (.svs) file format. The fifteen donor

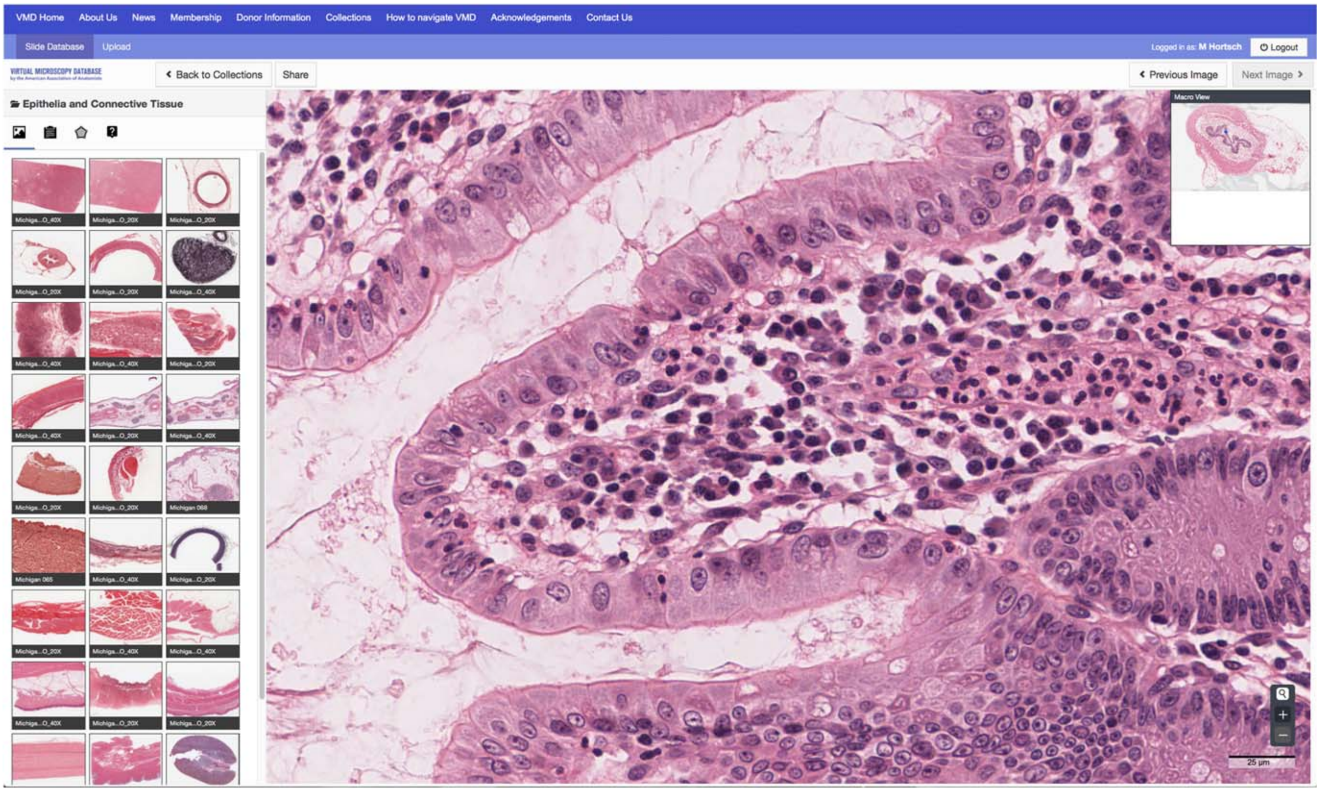

Figure 2.

A screenshot of a VMD virtual tissue slide from the University of Michigan collection (Michigan Slide #29-1). The Biolucida® viewer allows VMD users to examine the virtual image at different magnifications. The insert in the right upper corner is a navigational thumbprint of the entire slide with a box indicating the magnified area.

universities are located in the United States, Canada, Australia, and the United Kingdom. The copyright of all images in the VMD remains with the donating individuals or institutions, and all VMD image files are made available to other VMD users under an attribution-share alike-noncommercial Creative Commons license (CC, 2018). This license excludes any commercial use of VMD images without the written permission of the copyright holder.

Most of the virtual microscopy files in the VMD contain some supplementary information, such as the type of histological stain used and the organ and species from which the tissue section originated. Such information is crucial for VMD users to find and access histological structures or organs of interest quickly and to facilitate its effective use in research and/or for education. Currently, the majority of VMD images represent either light or transmission electron micrographs (TEM) of normal cells, tissues and organs. Pathological and immunohistochemically stained virtual image files currently comprise only a small sample in the VMD. Most virtual microscopy images in the VMD are from primate tissues, and some images are from other vertebrate animal species. At present, only one collection from the Tufts University's Cummings School of Veterinarian Medicine offers pathological slides of domestic animals. The incorporation of more diverse virtual microscopy images from different species, pathological samples, and the acquisition of scanning electron micrographs (SEM) will be a priority for growing the database in the future.

At this time, the VMD has over 550 registered users from 62 different countries around the world. The majority of VMD users have a college or university affiliation and a few are associated with scientific foundations or museums. Fifteen VMD users identified themselves as teachers at K-12 schools. All accepted VMD users have unrestricted access to all virtual microscopy image files in several different ways. Users may locate specific images/image topics by (1) perusing each of the 15 university collections and viewing the thumbprints of the images in the collection's subfolders or by (2) using a database-wide search function with keywords of their choice (Fig. 1). Once a virtual microscopy image of interest has been identified and selected, the integrated Biolucida® viewer (MBF Bioscience Inc., Williston, VT; Biolucida, 2018) allows the user to get a general survey of the slide or to view the image in more detail (Fig. 2). An area of interest within the selected virtual tissue slide may be saved as an image file by screengrab, or the user may select to download the entire virtual image file for local use. For educators wishing to use the VMD image files for student education, it is recommended to download and save the desired VMD files on a local computer server and to allow students access via a local network. A number of virtual slide viewers that can be installed on students' computers and computer tablets are available on the Internet or at app stores and some can be downloaded free of charge.

VMD image files can be used in many different ways, such as for lecture illustrations, for students' laboratory sessions, for the creation of supplementary course material, for the generation of quiz and examination questions, and other educational purposes. Virtual Microscopy Database image files can also be used for non-profit research projects, for example, for the development of histological slide scanning and recognition technology, the morphometric analysis of micrographs and more. Any use of VMD images is only restricted by the Creative Commons license as described above.

DISCUSSION

As the VMD has been in existence for less than a year, it is still a work in progress. Based on past, current and future demands, the VMD resource is projected to continue its growth not only in size and variety of images but also by indexing available image files for a more streamlined access and better user experience. Currently, the majority of VMD files are virtual microscopy images from normal tissues thus expanding the database with human and veterinarian pathology collections and SEM images, all accompanied by appropriate annotations, will be a priority in the near future.

The greatest strength of the VMD is the availability of a large number of high quality virtual microscopy images to its users. The diversity and multiple examples of histological variations available in the VMD collections will enable histology and pathology educators to elevate the quality of their teaching by exposing their students to a broader variety of images and by experimenting with new pedagogical techniques in their classrooms. The use of virtual microscopy for the teaching of histology and pathology has been shown to facilitate the introduction of active and collaborative learning approaches (Lei et al., 2005; Goldberg and Dintzis, 2007; Brown and Kearns, 2008; Husmann et al., 2009; Triola and Holloway, 2011; Bloodgood, 2012, Sander and Golas, 2013; Tian et al., 2014).

One of the restrictions of the VMD at present is the limited number of image file formats that are compatible with the VMD framework. Fortunately, the most common virtual microscopy file format, (.svs), is compatible with the VMD software and thus most image file donors will not experience difficulties in sharing their image collections. However, (.svs) files generated by older software or new file formats obtained using a whole slide scanner with a proprietary viewing software may not be compatible with the VMD, thus posing as a barrier for donors to share their resources via the VMD. Although image file conversion software is readily available, the transformation of a large number of image files is a time-consuming and cumbersome task.

Another obstacle for the advanced use of a resource such as the VMD is the requirement for a local basic technical infrastructure. Depending on the type of use, fast Internet speed, a local server network, a minimum bandwidth requirement, and access to computers and/or computer tablets for teachers and students are necessities. However, such hardware and technology-related resources are becoming more and more standard, even at schools in developing countries. This makes histology/pathology education using virtual microscopy feasible at almost any institution and the use of the VMD resource more far-reaching and effective.

With the recent Food and Drug Administration (FDA) performance recommendations for whole slide imaging systems for the purpose of pathology diagnosis (Federal Register, 2016), the wave of virtual microscopy adaptation is likely to take over the clinical realm as well, just as it did with histology and pathology education. The potential of virtual microscopy to advance clinical collaboration and diagnostics is another great opportunity for the VMD (Weinstein, 2005; Graham et al., 2009; Ghaznavi et al., 2013; Farahani et al., 2015).

Lastly, funding for the maintenance and upkeep of the VMD is a potential concern that needs to be addressed. The generous funding from the Innovations Program of the American Association of Anatomists and the corporate support by MBF Bioscience Inc., has made the VMD creation and its initial operation possible. However, running an ever-increasing database and a website of this size and complexity will require a long-term financial strategy. The VMD administrative team is currently exploring multiple avenues to support the VMD for the long-term and to keep VMD access free of charge.

CONCLUSIONS

The Virtual Microscopy Database (VMD) is a new, Internet-based, resource-sharing website for histology and pathology image files. The VMD allows its users, mainly educators and researchers, to make their virtual microscopy image files available to others and to have access to collections donated by other individuals and institutions. Therefore, the VMD is facilitating the use of virtual microscopy for research and teaching. A large number of user applications from around the world have been received since the launch of VMD site, indicating a global demand for such a resource. The VMD also holds a great potential for elevating the quality of histology and pathology instruction and making these subjects more accessible to students at educational institutions worldwide.

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NOTES ON CONTRIBUTORS

LISA M. J. LEE, Ph.D., is an associate professor in the Department of Cell and Developmental Biology at the University of Colorado School of Medicine, Aurora, Colorado. She has been teaching Histology and Embryology to medical, dental and graduate students for over 10 years and has developed

two virtual microscopy laboratory applications and her research interests focus are in human–computer interactions in education and in effective digital learning interface design and outcomes.

HAVIVA M. GOLDMAN, Ph.D., is an associate professor in the Department of Neurobiology and Anatomy at Drexel University College of Medicine, Philadelphia, Pennsylvania. She has a background in digital imaging and microscopy related to her research in bone biology. She has been teaching medical histology and anatomy for over 15 years and has developed numerous digital resources utilizing virtual microscopy for integrated anatomical education.

MICHAEL HORTSCH, Ph.D., is a professor in the Departments of Cell and Developmental Biology and of Learning Health Sciences at the University of Michigan Medical School in Ann Arbor, Michigan. Since 1991 he has taught medical, dental and graduate histology at the University of Michigan. He is interested in the development of novel electronic teaching tools and his research addresses how these new resources impact students' learning.

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