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Review of Telemicrobiology

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Abstract

Context—Microbiology laboratories are continually pursuing means to improve quality, rapidity, and efficiency of specimen analysis in the face of limited resources. One means by which to achieve these improvements is through the remote analysis of digital images. Telemicrobiology enables the remote interpretation of images of microbiology specimens. To date, the practice of clinical telemicrobiology has not been thoroughly reviewed.

Objective—Identify the various methods that can be employed for telemicrobiology, including emerging technologies that may provide value to the clinical laboratory.

Data Sources—Peer-reviewed literature, conference proceedings, meeting presentations, and expert opinions pertaining to telemicrobiology have been evaluated.

Results—A number of modalities have been employed for telemicroscopy including static capture techniques, whole slide imaging, video telemicroscopy, mobile devices, and hybrid systems. Telemicrobiology has been successfully implemented for applications including routine primary diagnois, expert teleconsultation, and proficiency testing. Emerging areas include digital culture plate reading, mobile health applications and computer-augmented analysis of digital images.

Conclusions—Static image capture techniques to date have been the most widely used modality for telemicrobiology, despite the fact that other newer technologies are available and may produce better quality interpretations. Increased adoption of telemicrobiology offers added value, quality, and efficiency to the clinical microbiology laboratory.

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Introduction

The role of informatics in the clinical microbiology laboratory is growing, which includes the practice of telemicrobiology.(1) Telemicrobiology is the use of telepathology technologies within the subdiscipline of clinical microbiology. Telepathology allows a human interpreter to have access to a digital image at a time or location that is separated from physical access to the specimen. The digital image can be a macroscopic picture (e.g. gross pathology, culture plate) or microscopic image (e.g. histopathology, special stain of microorganisms). The telepathology system in simplistic terms requires a mechanism for image acquisition, telecommunication link for image transmission and/or access, and a mechanism (display) to remotely review and interpret these images.

Telepathology has been successfully used for clinical purposes such as remote interpretations (telediagnosis) and second opinions or consultations (teleconsultation), as well as for non-clinical uses including educational purposes. In practice, telepathology has been largely employed in anatomical pathology. As a result, there is a large body of literature devoted to the use of telepathology for intraoperative frozen sections, teleconsultation for second review of histology slides, and telecytology for rapid on-site evaluation. More recently, the benefits of telehematology for remote interpretation of digital peripheral blood smears has been revealed. However, telepathology is also applicable to other areas of the clinical pathology laboratory where images may be of value, such as microbiology (macroscopic images of culture plates, and microscopic images of microorganisms) and chemistry (macroscopic images of gels, and microscopic images of fluids including urinalysis).

To date, only a few published articles mentioned the use of telepathology in the field of microbiology. Despite this paucity of literature, several successful telemicrobiology consultation services have been established such as the Centers for Disease Control and Prevention's (CDC) Division of Parasitic Diseases and Malaria's service for diagnostic assistance (DPDx). The scope of this review is to evaluate different applications of telemicrobiology that relate directly to the clinical microbiology laboratory including primary diagnosis, teleconsultation, and proficiency testing. Non-clinical applications of telemicrobiology for research and educational purposes are not discussed.

Technology for Telemicrobiology

Telemicroscopy can employ a number of modalities.(2) The most common modes of telemicroscopy include using static capture techniques, whole slide imaging (WSI), video telemicroscopy (VT), or a hybrid of these. Of these modes, static image capture is the most technologically rudimentary mode, but because it is inexpensive and easy to implement static imaging (store and forward) has been the most commonly used. Static capture telemicroscopy only requires a microscope with an attached digital camera and a means to

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share a relatively small digital image file (e.g. email or remote server). More sophisticated equipment is required for WSI and VT. However, these more advanced microscopic imaging technologies provide unique advantages such as access to an entire glass slide (Table 1). Most WSI scanners are not yet capable of digitizing glass slides using 100x oil-immersion magnification (Figure 1), which is a major drawback since 100x magnification is often used in clinical microbiology microscopy.

The benefits and limitations of WSI as a modality in surgical pathology have been discussed elsewhere.(3-6) With respect to WSI use for telemicrobiology, important issues to be addressed are the capability of these devices to produce digital slides at high enough magnification and with sufficient depth of field (z-stacking) to be able to easily discern microorganisms. Traditionally, depth of field (focusing) is limited in WSI. As a result, WSI with most of the commercially available scanners is routinely performed at a resolving power less than is used in routine clinical microbiology. Microbiologists often view slides using a 100x oil-immersion objective lens, whereas WSI in anatomical pathology is typically performed using only 20x or 40x magnification; the latter magnification is typically used for scanning cytology or hematopathology slides. Some authors have suggested that employing this lower power magnification for WSI may be inadequate to confidently rule out the presence of microorganisms, such as *Helicobacter pylori* even with immunohistochemical staining.(7) However, it has been demonstrated by other investigators that when using WSI with a 40x objective and capturing multiple Z-dimensions, the digital slides produced have the equivalent diagnostic potential for identifying *H. pylori* in gastric biopsies (not stained with immunohistochemistry) to examining a glass slide using a traditional microscope.(8)

Clinical Microbiology Applications

Telemicrobiology has been used for multiple applications in clinical testing. These applications include the routine use of telemicrobiology as part of daily operations, use of telemicrobiology for internal consultations within a health system, and use of telemicrobiology for external consultations. More than a decade ago, the German Army Medical Service began developing and implementing telemicrobiology services including telebacteriology, teleparasitology, and televirology for routine daily use in its field laboratory operations.(9, 10) In the late 1990s, Veterans Integrated Service Network (VISN) 12, which is part of the Veterans Health Administration in the USA, began feasibility tests and implementation of a telepathology system to connect its medical centers.(11) This network was used for telemicrobiology consultative services within the VISN.(11-13) In 1998, the Centers for Disease Control and Prevention's (CDC) Division of Parasitic Diseases and Malaria's service for diagnostic assistance (DPDx) began practicing teleparasitology, which pathologists from all over the world now use as an external consultative service. Recently, a growing number of laboratories have been exposed to telemicrobiology through the use of digital samples for proficiency testing. Another emerging and quickly growing application of telemicrobiology is digital plate reading, which is the use of digital images of bacterial culture plates for intralaboratory analysis. With the ubiquitous use of the Internet and mobile devices, we are beginning to witness more mobile health applications of telemicrobiology.

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Telemicrobiology for Routine Work

Scheid and colleagues reported their clinical experience using telemicrobiology in German Army Medical Service field microbiology laboratories.(9) Their initial work involved telebacteriology (e.g. assessing bacterial plate cultures) and teleparasitology (e.g. diagnosing malaria, leishmaniasis, and foodborne parasites such as worm ova) in 2002 and 2003, followed by examination of cell cultures for televirology in 2005 and 2006.(10, 13) Their system employed two microscopes, one for high-powered examination of cells and one for low-powered examination of colony morphology on nutrient media. They used a digital camera to capture 1360 × 1024 pixel images.(10, 13) DISKUS software (Hilgers, Königswinter) was used to process, transmit, and archive their images; and it enabled a remote expert to measure objects in the photomicrograph. After transmission of the photomicrograph(s), a video conference between the expert and the laboratory photographer was commenced to discusses cases.

This group performed a variety of validation studies in which the photographer and the interpreter were both blinded.(9) Malarial smears, stool examination for parasites, Gram stains of bacterial suspension, Gram stains of colonies, Gram stains of specimens from various sources, and colonies growing on nutrient media were all analyzed in this blinded fashion. The photographers had limited microbiology experience and were described in the study as “medical assistants,” whereas the interpreters were bacteriologists and parasitologists. This telemicrobiology system enabled the expertise of microbiologists to be used remotely in field laboratories where microbiology expertise was limited. Not surprisingly, the remote microbiologists provided more accurate interpretations than the on-site assistant.

As is the case with most store-and-forward telepathology setups, the importance of the photographer in selecting appropriate fields of view for capturing representative images is of “decisive importance.” The photographers “cannot transmit what they do not notice,” and the inexperience of photographers was deemed a “limiting factor” by Scheid.(9) In some instances, such as parasitological stool diagnosis, the sensitivity of testing was as low as 72%, which the authors attributed to the photographer submitting nondiagnostic images to the expert for interpretation. The authors state that telemicrobiology “is not a replacement for adequately trained staff,”(9) and they emphasize that all laboratory persons using the telepathology system should be trained in a central location using identical equipment to what is used in the field.(10, 13) This training not only prepares assistants for field work, but ensures that the experts who train the assistants personally know the field staff.(10, 13) Overall, Scheid and colleagues concluded that their telemicrobiology system “provided significant benefits to the health of deployed German forces.” The North Atlantic Treaty Organization is also encouraging the use of this type of telemicroscopy to extend microbiology services and to help decrease the number of deployed medical staff.(14)

Telemicrobiology for Internal Consultation

The Veterans Health Administration (VHA) Veterans Integrated Service Network (VISN) 12 contains eight Veterans Administration Medical Centers (VAMCs) that are connected via a telepathology network.(11) McLaughlin and colleagues reported the feasibility of

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telemicrobiology among these VAMCs in 1998.(13) In this study, the authors explored the use of static digital photomicrographs to interpret Gram stains of specimens such as sputa, stools, and wounds. In their study, three pathologists examined 30 cases. Each case consisted of a pair of 1024 × 768 pixel images, one of which was captured using a 40x objective lens and one of which was captured using a 100x objective lens. The pathologists also examined the actual glass slide from each case using a conventional light microscope. They reported that the accuracy of static telemicrobiology was on par with the interpretation of glass slides; 95% of samples from each mode produced no major discrepancies.(13) Interpretation of the digital images took half the time (2.1 minutes) compared to examining glass slides (4.3 minutes). However, it took about 15 minutes to digitally capture each case. So, while analysis time by the consulting pathologist was reduced when using telepathology, the total time required for each case was greater.

Several reasons that may account for discordant interpretations when using telemicrobiology for the remote analysis of Gram stains, all of which occurred in McLaughlin's study:

1) Poor field selection by the photographer, which decreased the sensitivity of the interpretation.

2) Poor image quality, which compromised the accuracy of interpretation.

3) Too few fields photographed, which resulted in diagnostic uncertainty by the interpreter.

4) Inappropriate case identification by the interpreter, which resulted in mispairing of the case number and its interpretation.

The VISN-12 telepathology network includes both robotic and non-robotic telemicroscopy elements, using a hybrid of static capture and live video image acquisition.(12) The network is used by both pathologists and technologists. Images shared over the network include static micrographs of stained slides and macroscopic images of culture plates. Additionally, live dynamic video of wet mounted slides can be viewed to examine potential motility of microorganisms. Several points that are important for operational success, which they have learned since implementing this telemicrobiology system:(11)

1) Effective technological change requires enthusiasm and technical expertise at all sites.

2) When problems occur, it is imperative to have technical support rapidly available and to communicate directly and frequently with the parties involved.

3) Remote analysis requires careful attention to specimen preparation and examination in the same manner as is required for all laboratory work.

Telemicrobiology for Expert Consultation

The Centers for Disease Control and Prevention's Division of Parasitic Diseases and Malaria Diagnostic Assistance Service (DPDx) offers worldwide telediagnosis of parasitic infections. DPDx now receives more than 400 telediagnostic cases annually.(15) In total, DPDx has received more than 3,300 requests for telediagnosis from more than 60 different countries since it began accepting telediagnostic requests in 1999.(15, 16) Telemicroscopic

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consultations are advantageous because they can be completed more quickly and can cost 80% less than traditional diagnostic consultations.(17, 18) Images received by DPDx for consultation include mostly digital photomicrographs of blood and stool specimens, but images of tissue sections, arthropods, and worms have also been analyzed.(16, 18) DPDx's telemicroscopic consultations are performed within a CLIA-certified laboratory; therefore, these test requests are required to include much of the same information as any clinical laboratory would require, but additional information is also needed because of the unique approach of consult telemicrobiology (Table 2).(19) CDC laboratory staff can also access telediagnostic requests via secure mobile devices.(15, 17) DPDx has more experience than any other entity in performing consultative teleparasitology, which has a number of advantages and disadvantages over traditional parasitology consultation (Table 3).

From October 2005 through September 2009, about one-third (423/1192) of telediagnostic requests to DPDx were for the potential diagnosis of malaria.(18) Of these, about 70% resulted in a confident diagnosis (positive identification of *Plasmodium* to the species level, positive identification of *Babesia*, or negative for parasites), but physical samples were requested for the remaining 30% of telediagnostic requests in order to achieve a more confident or specific diagnosis. In instances in which this additional sample was received by DPDx after it was requested, a confident microscopic diagnosis of the infecting *Plasmodium* species could be made in 46% (36/79) of the samples. In some instances, physical specimens were received by DPDx even after a confident telediagnosis was made, although the physical specimens were not requested; and follow up testing of these physical specimens resulted in a diagnosis that was discordant with the original telemicroscopic diagnosis 7% (5/71) of the time. These findings demonstrate that telemicroscopic images sent to DPDx for malarial parasite identification usually yield a rapid and accurate diagnosis; but in this scenario, telemicroscopy is not as sensitive or specific for achieving *Plasmodium* species identification as traditional microscopy.(18) However, the rapidity associated with a DPDx consultation is essential in order to provide appropriate treatment in cases that might be fatal if not properly managed. For example, the morphologic similarities between *Babesia* and *Plasmodium falciparum* is a common pitfall for sentinel laboratories, which can lead to misdiagnosis and subsequent clinical mismanagement. Rapid and accurate differentiation between babesiosis and *P. falciparum* malaria has been achieved through DPDx telediagnosis.(17)

Proficiency testing

Currently, the College of American Pathologists (CAP) offers proficiency testing surveys that use telemicroscopy.(9) Some surveys (e.g. parasitology) use static digital images. Other surveys (e.g. virtual Gram stain and vaginitis screen) use WSI (http://www.cap.digitalscope.org/) for proficiency samples. There are several advantages to using telemicroscopy for proficiency test samples. Telemicrobiology ensures that all proficiency testing sites have access to the same quality of sample. Only a small amount of physical and potentially infectious sample is required, which can then be imaged and shared electronically with an unlimited number of laboratories. Telemicrobiology provides cost savings due to decreased postage, consumables, and preparation time needed. It also relieves the need for laboratories to keep track of a physical specimen. Disadvantages of using

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telemicroscopy for proficiency testing include using a method of analysis (visual digital image analysis), which is typically different from that which is used in routine laboratory testing. Moreover, digital image analysis requires a different workflow than what is used for physical specimens. For example, telemicroscopy bypasses testing the quality of the laboratory's preparation technique and microscope quality. The focus quality of the image is determined before it arrives to the laboratory, which may be limit interpretation, especially for images with only a single Z-plane. Nevertheless, the cost saving and specimen standardization advantages of using electronic samples for proficiency testing are two factors that will help ensure the continued and growing use of telemicrobiology in proficiency and competency testing.

Digital Plate Reading (DPR)

In addition to telemicroscopy, telemicrobiology may also involve the remote analysis of digital images of culture media, which is referred to as DPR. The emerging practice of DPR has been previously reviewed.(20) As described above, Scheid and McLaughlin have used custom-built systems for low throughput DPR. However, commercial high throughput DPR systems are currently being employed in some clinical microbiology laboratories, which aim to improve efficiency and quality. DPR systems enable a technologist to analyze bacterial culture plates remotely.(21) DPR systems require a front end component that can simultaneously incubate culture plates while employing automation to move the plates to an image capture station at defined time points. In this system, removal of the culture plates from the incubator is minimized, which helps to avoid delays, repetitive manual tasks, and exposure to suboptimal incubation temperatures. The images are analyzed and interpreted by microbiologists who view them on a computer display using proprietary software interfaces provided by the manufacturer (Figure 2). Work is being done to integrate digital images of Gram stains into this DPR analysis pipeline.(22) An initial report has demonstrated that DPR can help improve the productivity of microbiology technologists.(23) Although dozens of clinical laboratories, predominantly in Europe, have implemented DPR systems; peer-reviewed studies using these systems are needed. Copan, BD Kiestra and bioMeriéux are companies currently marketing digital plate reading systems for routine use.

Mobile Telemicrobiology

Many cellular telephones are now equipped with high resolution digital cameras and cellular Internet connectivity. This combination of features has fostered the rapid emergence of mobile telemicroscopy, including mobile telemicrobiology.(24-26) Mobile telemicrobiology offers hope of affordable, accurate, and rapid teleconsultation for developing communities worldwide.(27) The most commonly investigated uses of mobile telemicrobiology are in the areas of tuberculosis detection and parasite identification.

One of two general strategies are typically used in mobile telemicrobiology. One approach is to use a portable microscope and an unmodified cell phone camera. In 2011, Tuijn and colleagues used this approach. They described the utility of using mobile telephones containing cameras to capture and transmit microscopic images and short videos of pathogens such as *Plasmodium* spp., *Giardia*, and *Mycobacterium tuberculosis* (TB).(26) Their investigation concluded that cell phone cameras can capture and transmit images

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capable of verifying *Plasmodium* presence in blood smears and identifying the parasites to species, verifying bacterial vaginosis, verifying *Giardia* by viewing a video which captured its motility pattern, and verifying positive TB smears. Tapley and colleagues developed a prototype system that acts similarly to a cellular phone's camera and display screen to capture and display a fluorescent microscopy live feed.(28) They demonstrated that minimally qualified individuals could effectively use the system to interpret sputa for the presence of mycobacteria, and the authors suggest that this method could be enhanced by transmitting some of the images to remote experts. In 2009, Zimic and coauthors described the use of cellular telephones to transmit images of mycobacteria grown in a drug susceptibility test system.(29) These images were first captured with a digital camera, and then the data were transferred to a cellular telephone and transmitted via the phone to off-site experts for analysis. Presumably, if this study was performed today, the images could be capture directly onto a cell phone using the phone's camera. Zimic reported concordance of interpretation between off-site analysis of digital images and on-site direct microscopic analysis of the cultures in 74 of 75 instances, and the authors concluded that the use of cellular phones for transmitting images would facilitate the diagnosis of multi-drug resistant tuberculosis (MDR-TB) in settings where adequately trained staff is a limiting resource.

A second approach to mobile telemicrobiology is to modify an existing cell phone camera's lens to transform the phone's camera into a microscope. In 2013 and 2014, Bogoch and colleagues used this type of approach. They described the use of a simple 3 mm ball lens (Edmund Optics; Barrington, NJ, USA) taped to the iPhone 4S (Apple; Cupertino, California) camera lens that could be used directly on microscope slides containing stool preparations to detect worm eggs.(30, 31) In their studies, they analyzed the samples' images directly on the phone, but this method could easily be adapted to enable an expert to remotely view the cell phone camera's live video feed. Unfortunately, the modified cell phone camera provided very poor specificity (36%) when compared to using standard microscopy.(31) Switz and colleagues demonstrated proof of concept that a reversed lens in a mobile phone's camera can potentially perform better than a 6mm ball lens, and they demonstrated its ability to resolve an *Ascaris lumbricoides* egg with the help of image post-processing.(32) These studies did not attempt telemicrobiology, but remote analysis is a logical next step in these studies.

These types of mobile telemicroscopy systems have the potential to extend the ability to perform effective microbiology microscopy in resource-limited or remote settings that are lacking a highly qualified microbiologist. In such circumstances, difficult cases could be simply and rapidly sent for remote consultation via telemicrobiology. It remains to be seen if video (live or recorded) or static capture methods will be most effective when using cellular phones for capturing and transmitting microscopic images for telemicrobiology.

Future Directions

Using readily available commercial products and open-source software to build telemicroscopy networks may help overcome clinical microbiology infrastructure challenges that are present in resource-limited areas of the world. This may provide a mechanism to increase the capacity of disease monitoring through collaboration in these underserved areas,

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specifically in the realm of malaria diagnoses.(33) Some investigators have demonstrated that emailing static images of blood smears are sufficient to diagnose malaria and other parasites that have distinct diagnostic morphologic features.(34) Indeed, static telepathology for diagnosis and parasite identification is performed routinely as part of the services provided by CDC's reference diagnosis (DPDx). Such services will undoubtedly continue to play an important role in telemicrobiology in the future because many laboratories have limited on-site expertise in diagnosing rarely encountered parasitic infections.

Additionally, the frequency of routinely using interlaboratory telemicroscopy networks in resource-rich locations may also increase. As health systems work to centralize and consolidate microbiology laboratories, maintaining the skills and competency to perform STAT microbiology testing (e.g. blood culture Gram stains, spinal fluid microscopy, sterile tissue touch preparations, etc.) at satellite locations can be a challenge,(35) and the use of automated slide staining equipment(36) combined with telemicroscopy may fill a growing need in the consolidating microbiology laboratory.

As telemicroscopy equipment becomes more prevalent, less expensive and/or as mobile telemicroscopy platforms become more feasible, live video telemicrobiology consultation may become more routine. Real-time telediagnosis is a promising area of application that could enhance the diagnostic capabilities of telemicrobiology consultation, such as the DPDx system. This approach would allow the submitting laboratory to provide a live feed to the consultant, and the consultant would be able to guide the microscope operator and discuss the case in real-time. Services such as DPDx could be used to support more global and environmental health needs if properly implemented. For example, remote parasitology services could be used to expedite the identification of causative agents (e.g. cyclposporiasis or trichinellosis) from clinical, environmental, and/or food samples during outbreak investigations.(37, 38) Some areas of the world face constant health threats but lack the expertise that is required to provide optimal diagnostic care. Developing an infrastructure that would enable these areas to gain access to services such as DPDx could greatly improve the areas' healthcare, but establishing and maintaining front end quality (e.g. proficiency training) and functional systems (e.g. maintained devices and connectivity) have to be considered and supported if this type of investment to strengthen global disease detection is pursued.

Others are working to hack cellular telephones into portable telemicroscopy instruments capable of capturing, analyzing, and transmitting diagnostic images from sputa or blood smears for telemicrobiology consultation(27, 39) or for reference by the treating clinician.(40) Widespread adoption of cell phone cameras may foster an increase in the amount of telemicrobiology consultation. Crowdsourcing and gamification of microscopic identification of infectious agents, such as *Plasmodium*, has been investigated.(41-43) It is difficult to imagine this approach to telemicroscopy gaining traction in the current era of patient privacy vigilance and analyst credentialing requirements, but it is a novel contemporary approach to disease screening and diagnosis.

Telemicrobiology is a strategy that can be used to expedite interpretation or improve interpretation of microbiology images. However, another approach that can be used to

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accomplish these goals is the use of computer-augmented image analysis (CAII) software. CAII has been successfully applied to routine cytopathology analysis to facilitate automated Pap test screening. In the clinical laboratory, CAII is routinely used in some hematology(44) and urinalysis(45, 46) testing, but CAII is not yet routinely used in clinical microbiology. In microbiology, CAII studies have been performed, which interrogate the software's quality in screening slides for mycobacteria, interpreting Gram stains, counting bacterial colonies, and detecting parasites. The most extensive body of work is in the development of automated image analysis tools to detect and characterize malarial parasites in blood smears.(47-53) There is interest in implementing CAII for use in routine clinical microbiology,(54) and some have partnered cell phone camera image collection with CAII.(55) Novel portable microscopes may one day be used to detect parasites directly from samples by using CAII, which would decrease the need for off-site expert analysis using telemicrobiology.(56, 57) Consumers' and software developers' growing interest in affordable, modular app-based software designed for mobile platforms may facilitate the adoption of CAII on mobile devices and will likely augment human telemicrobiology consultation in the future (Figure 3).(58)

Conclusion

Telemicrobiology systems can be effectively used to increase the speed and/or quality of microbiology visual data interpretation. Only a couple of complete telemicrobiology systems have been described, which were built for routine use.(9, 13) These complete systems were custom-built, primarily used static imaging, and proved to be effective in accomplishing their goal of remote expert microbiology analysis. Laboratories have used remote expert analysis for routine daily operations, for consultation within a health system, and for external expert consultation. Those who have used telemicrobiology for clinical testing have recognized that the screening quality of the person who acquires the visual data can limit the sensitivity of the analysis. The use of an alternate telemicroscopy method, such as WSI may improve the sensitivity and accuracy of routine telemicrobiology because WSI enables the off-site expert to access the entire slide and identify the most diagnostically relevant area of the slide instead of relying on the on-site photographer.

Other telemicrobiology systems have been implemented for discrete applications within the laboratory, such as proficiency testing or DPR. The use of telemicrobiology in proficiency testing and plate reading is expected to continue to grow. Proficiency testing has been able to standardize assessments through implementing telemicrobiology. Studies have been performed to interrogate the utility of cellular phones and their cameras for capturing and transmitting microbiology visual data, and the greatest incentive for implementing these platforms is in resource-limited settings. Going forward, computer analysis of digital images will likely augment human analysis in the telemicrobiology workflow.

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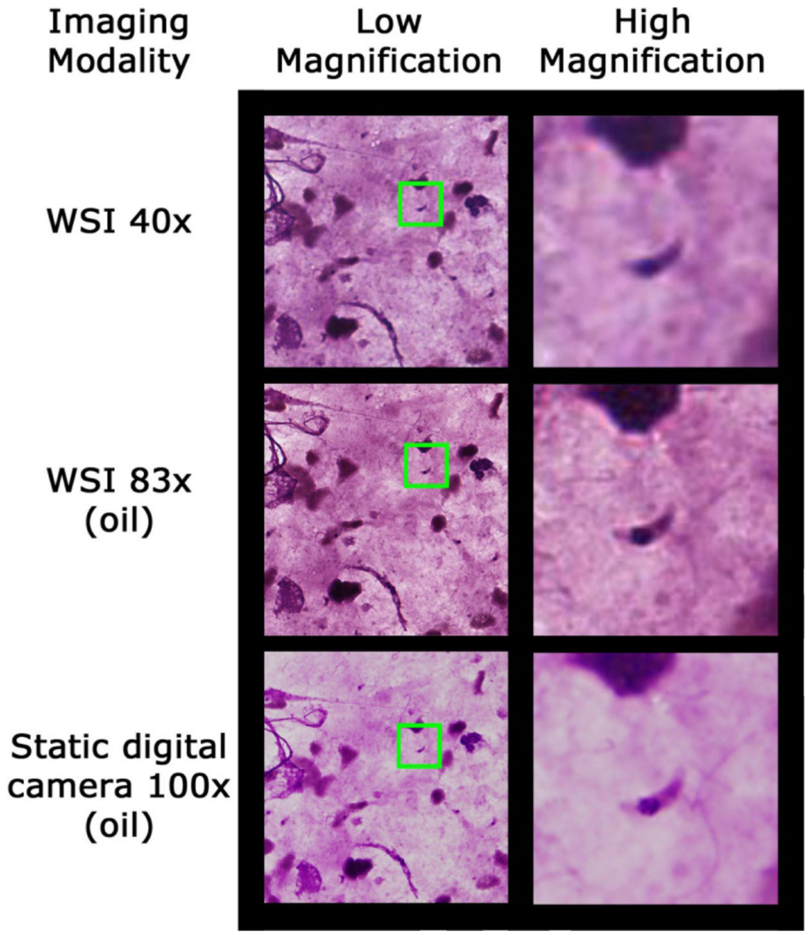

Figure 1.

A bronchoalveolar lavage cytospin with toxoplasmosis is shown (Romanofsky stain). Three imaging techniques were used to digitize the glass slide to create this comparative figure including 40x whole slide imaging (WSI) using the Aperio ScanScope XT (top row), 83x oil-immersion WSI using Aperio CS-O (middle row), and a 100x oil-immersion static image captured using an Olympus U-TV0.5XC-3 camera (bottom row). At low magnification (left column) all of the images appear to be of similar quality. However, when viewing a *Toxoplasma* tachyzoite at higher magnification (right column) there is a marked difference. In the 40x WSI image (top right), the tachyzoite's nucleus is difficult to resolve when maximally zooming in on the image. In the 83x WSI image (middle right), the nucleus is clearly visible, but nuclear details are still not entirely evident. In the 100x static capture image (bottom right), the nucleus is clearly visible, and some nuclear detail is evident. (The 83x images were generously provided by Mohamed E. Salama, MD.)

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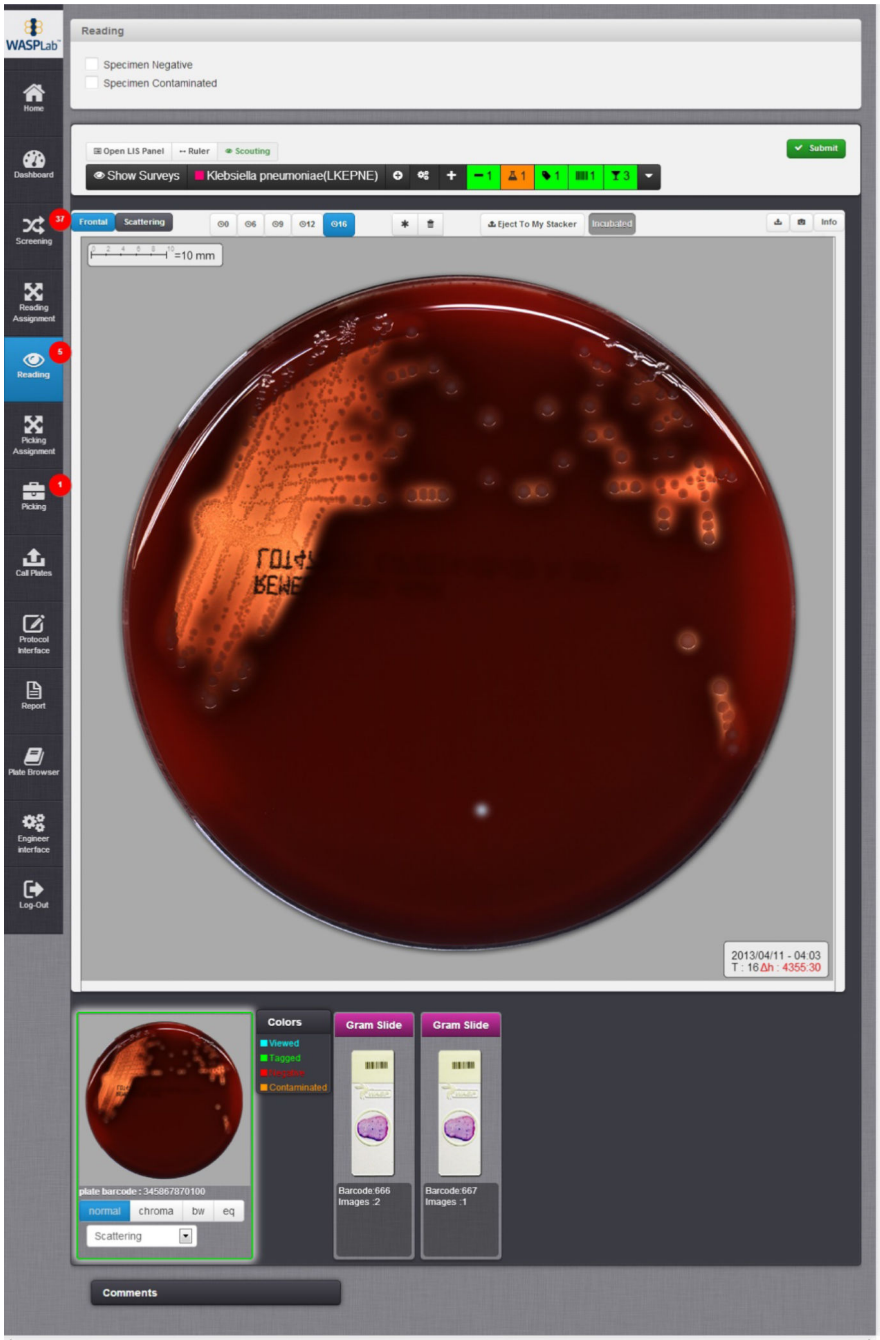

Figure 2.

Copan's WaspLAB software interface for digital plate reading. The software displays a digitally photographed culture plate and provides tools to annotate and analyze the image. Thumbnail images of the Gram stained specimen are visible at the bottom of the browser window, and these slides are meant to be viewed using the same software interface. Image is courtesy of Copan.

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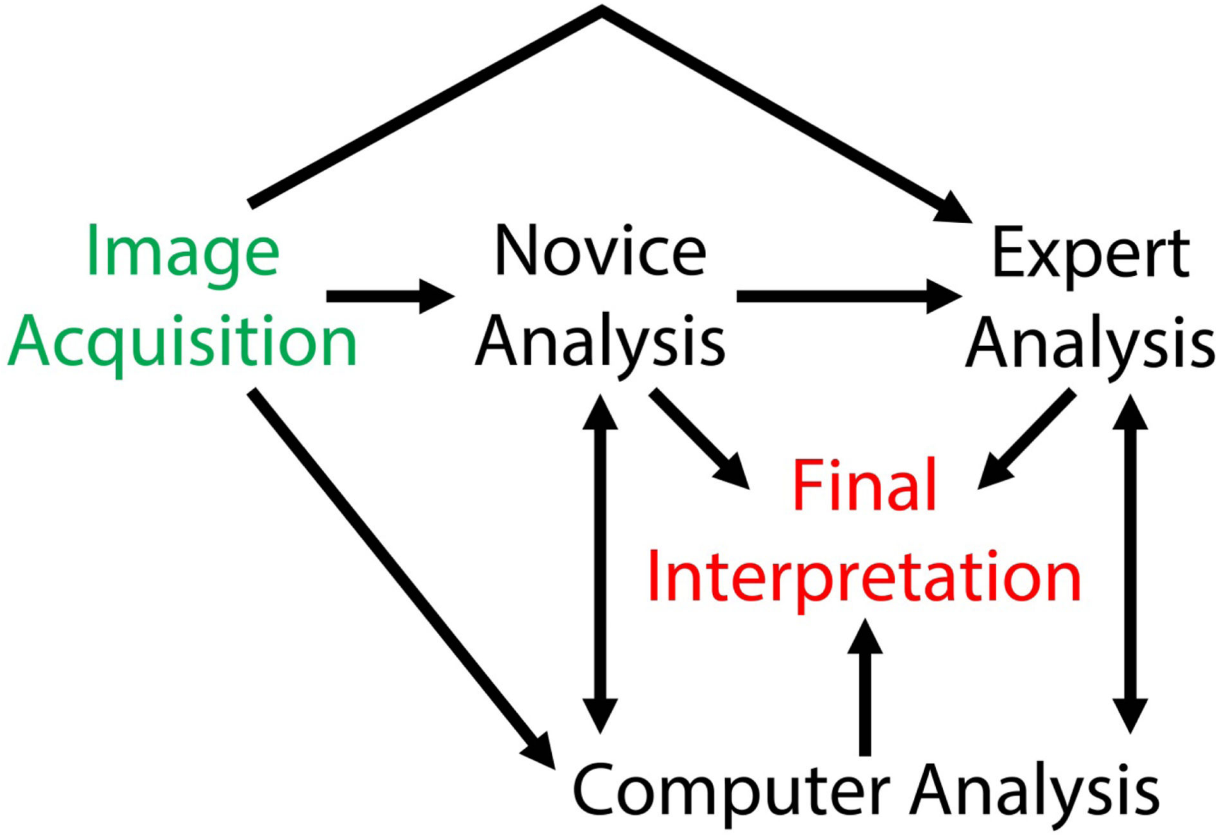

Figure 3.

The workflow of a telemicrobiology system begins with image acquisition (green) followed by a number of possible analysis pathways (black) and then a final interpretation (red). Typically, image acquisition and novice analysis is performed at the same physical location and does not incorporate the use of telemicrobiology. Telemicrobiology is used when consulting an off-site expert. Currently, computer analysis is not routinely used, but in the future computer analysis is likely to be a valuable resource to enhance the quality and/or speed of digital image analysis that can be performed by on-site novices and off-site experts.

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Table 1

Comparison of different telemicroscopy modalities

	Static image capture	Live human-operated video	Live robot-operated video	Recorded video	Whole slide imaging
File created (Image can be analyzed after slide has been filed)	Yes	No	No	Yes	Yes
File size	Megabytes	N/A	N/A	Variable	Gigabytes
Bandwidth demand	Low	Moderate	High	High	High
Time required for image generation	1-10 minutes	Instantaneous	Instantaneous	1-10 minutes	10-100 minutes
Image area (X-Y dimensions)	Minimal	Maximal	Maximal	Variable	Maximal
Image depth (Z-dimension)	Minimal	Maximal	Maximal	Maximal	Variable
On-site expertise required for screening	Yes	Yes	No	Yes	No
Capital equipment costs	Minimal	Moderate	Maximal	Moderate	Maximal
Maximum objective lens magnification	100× (oil)	100× (oil)	60× (possible with some scanners)	100× (oil)	Up to 83× (possible with some scanners)

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Table 2

Information required by DPDx when requesting telediagnosis and the importance of these data.

Information required for sample submission	**Importance of information required**
Multiple images of the suspected parasite	Facilitates ease and accuracy of telediagnosis
Pertinent patient history (including travel history)	Helps direct differential diagnosis
Suspected diagnosis	
Type of specimen	Objective information about the sample source, its preparation, and the captured image facilitate analysis
Date of collection	
Stain used	
Lens magnification used	
Two unique patient identifiers	Linking a specimen to the correct patient, test ordered, and ordering physician is necessary in telemicrobiology in the same way it is important in all clinical laboratory testing
A standardized requisition form (http://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf)	

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Table 3

Advantages and disadvantages to static-image teleparasitology as performed by the CDC-DPDx

Advantages	Disadvantages
Rapid identification or screening (usually within an hour or two). Clinically relevant examples: • Differential identification of organisms where treatment differs (e.g. differentiating *Babesia* and *Plasmodium*) • Recognize or rule-out acutely life-threatening pathogens (e.g. free-living amoebae) • Identification of organisms where there may be infection control needs (e.g. nosocomial *Sarcoptes scabiei*) • Determination of when follow-up is warranted for further molecular analysis (e.g. discriminating *Entamoeba histolytica* vs. *E. dispar*, resolving *Cyclospora* to species level for outbreak investigations, confirming the presence of amastigotes in suspect cases of leishmaniasis, or characterizing extraintestinal microsporidiosis) • Investigation of potential infection via transfusion or transplant (e.g. *Babesia* in a blood recipient)	Submission of images may be biased based on the presumptive diagnosis of the submitter (e.g., submitting only images of features that support the presumptive diagnosis and not giving a clear overall picture of the case). Static images do not provide multiple Z-planes, which can impair the quality of the analysis in some cases (e.g. quantifying *Entamoeba* nuclei, visualizing both the nucleus and kinetoplast in *Leishmania* or *Trypanosoma cruzi* amastigotes). The quality of the consultant's interpretation can be limited by the poor quality of the submitter's images. Common examples that render images unsatisfactory for analysis include: • Poor focus • Poor magnification choice for the suspected organism • Poor image exposure (e.g. overexposure) • Poor cropping • Too few images submitted to give a clear overall picture of the case
Less expensive than traditional specimen submission (i.e. physically mailing slides and/or related materials). No risk of physical damage to the specimen (e.g. slide breakage) or permanent specimen loss (e.g. fluid leakage). Avoids shipment of and potential exposure to potentially infectious pathogens. Diagnoses are reported in accordance with CLIA guidelines.	The quality of the consultant's interpretation can be limited by the submitter's omission of important data regarding the submission (e.g. size, magnification, specimen type, stain used, relevant travel history). Some organisms are inherently difficult to image well. For example: • Amastigotes of *Leishmania* sp. or *T. cruzi* in tissue sections • Microsporidia • Coccidian protozoa • Adult (gross) helminths
Facilitates information sharing and training including: • DPDx image library • DPDx monthly case studies and other teaching resources • Publications	