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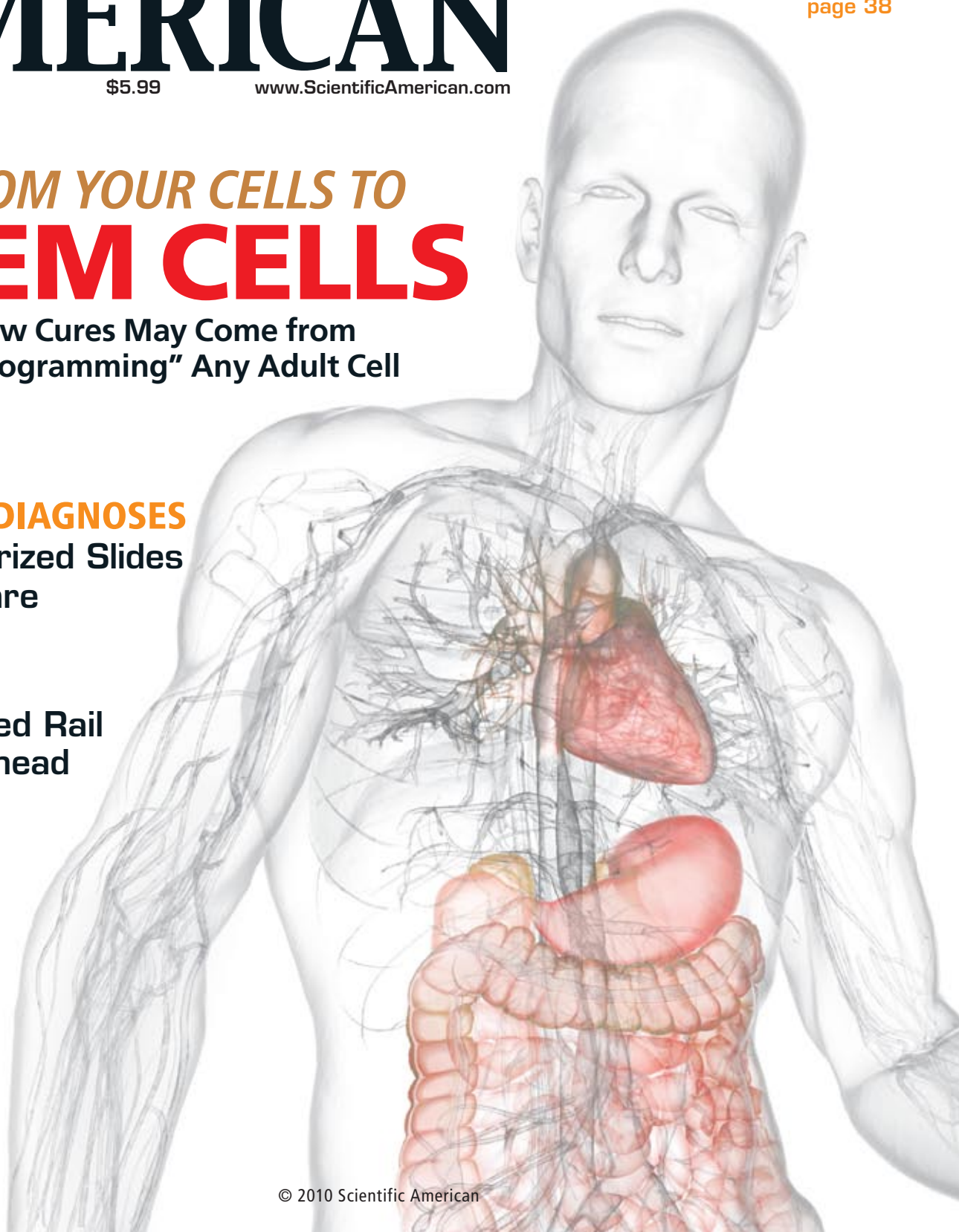


A Better Lens on DISEASE

Computerized pathology slides may help doctors make faster and more accurate diagnoses

BY MIKE MAY

KEY CONCEPTS

- A remake of pathology, a profession that has processed samples the same way for more than 100 years, is long overdue.
- Emerging techniques allow computerized images of biopsies to be manipulated in novel ways.
- Ultimately, digital pathology will allow for more precise diagnoses of tissue samples, whether from an oncologist's office or a crime scene.

—The Editors

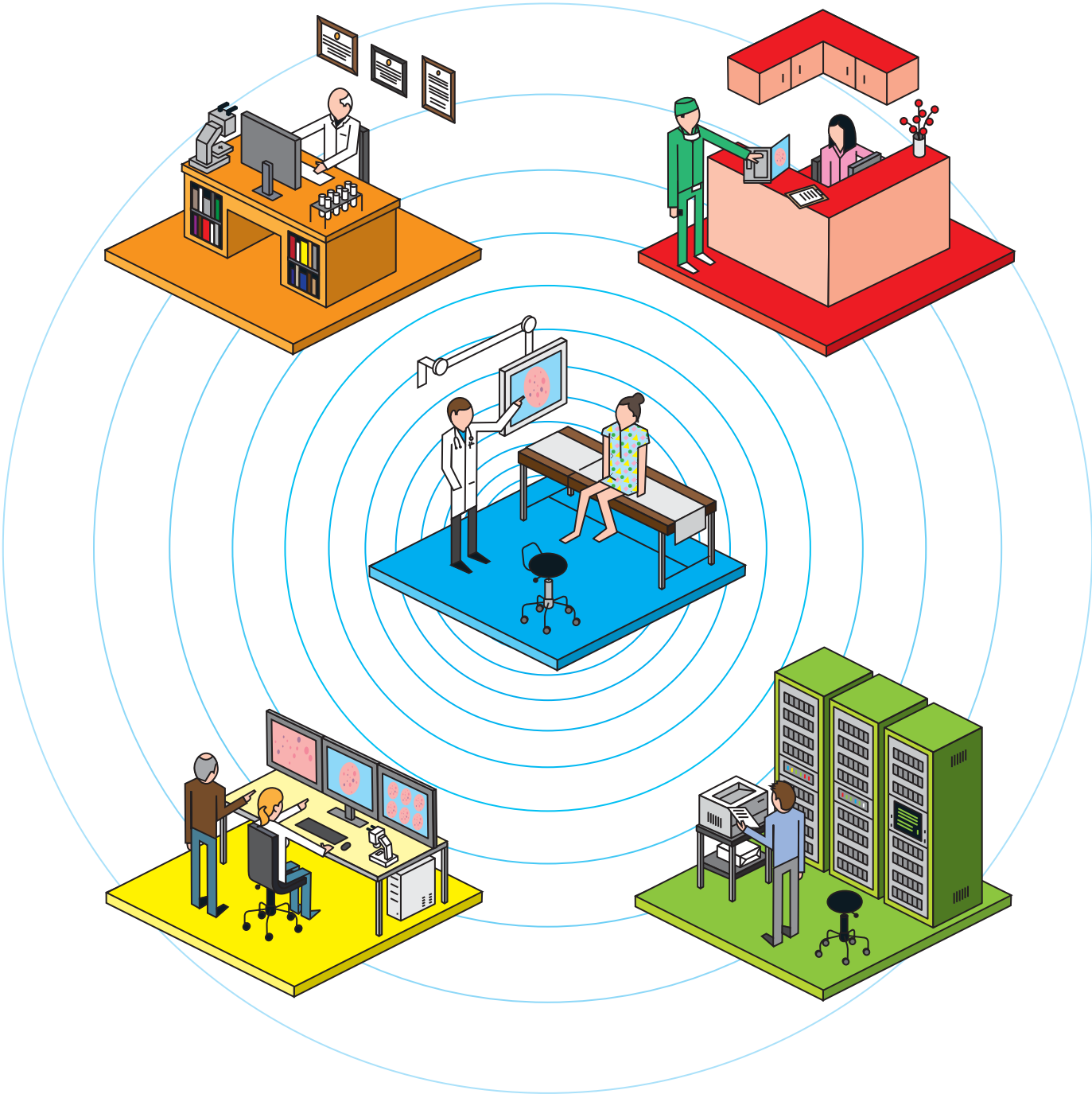
In the late 1990s Dirk G. Soenksen imagined a new future for pathology. At the time, pathologists often sat on telephone books to get a good view through their microscopes, yet Soenksen's children viewed high-resolution monitors when merely playing Nintendo. "Why can't microscopists look at computer monitors, too?" he wondered.

That question sent Soenksen on an extended journey, beginning in his garage. After 18 months of intense laboring, he emerged as the head of a newly created digital-pathology company called Aperio, which he now runs in Vista, Calif. Beyond merely moving images of diseased tissues from microscopes to computers, his technology—as well as that of other start-ups and even established health care companies—promises to make anatomical pathology, which involves the interpretation of biopsies, far more quantitative. This advance should, in turn, enhance the accuracy of diagnosing diseases and help physicians track the effectiveness of a treatment so that any needed changes can be made promptly.

Most pathologists already use computers in some way, if only to make notes in patient files. Beyond a computer monitor, assorted notepads and piles of papers usually cover a pathologist's desk. Only a research pathologist, however, is likely to be able to inspect a sample as a digital file. In general, today's pathologists lack the ability to make or obtain digitized slides, and review of such slides is approved by the U.S. Food and Drug Administration for only a few medical applications, all related to breast cancer.

For now, the hundreds of millions of pathology slides prepared annually get handled as they have for more than 100 years. A tissue sample gets cut into paper-thin, or thinner, sections, and a stain brings out specific features. Then, a pathologist puts the glass slide under a microscope. In a breast cancer biopsy, for example, a pathologist looks for a range of features in the tissue, including the number of abnormal cells in the section and the tumor grade, the latter depending on features such as cell structure. "Now this is done by eyes over the microscope, looking at every little point," says George K. Michalopoulos, chair of the department of pathology at the University of Pittsburgh.

In fact, pathologists do not look at every spot on every slide, but digitized versions could be inspected more thoroughly. A computer could analyze each pixel on every digital slide. And it could find and measure attributes indicative of health and disease—such as internal structure, color, texture and intensity of every pixel in ev-



ery cell. A pathologist hunched over a microscope would assess those same attributes in only a small number of the cells.

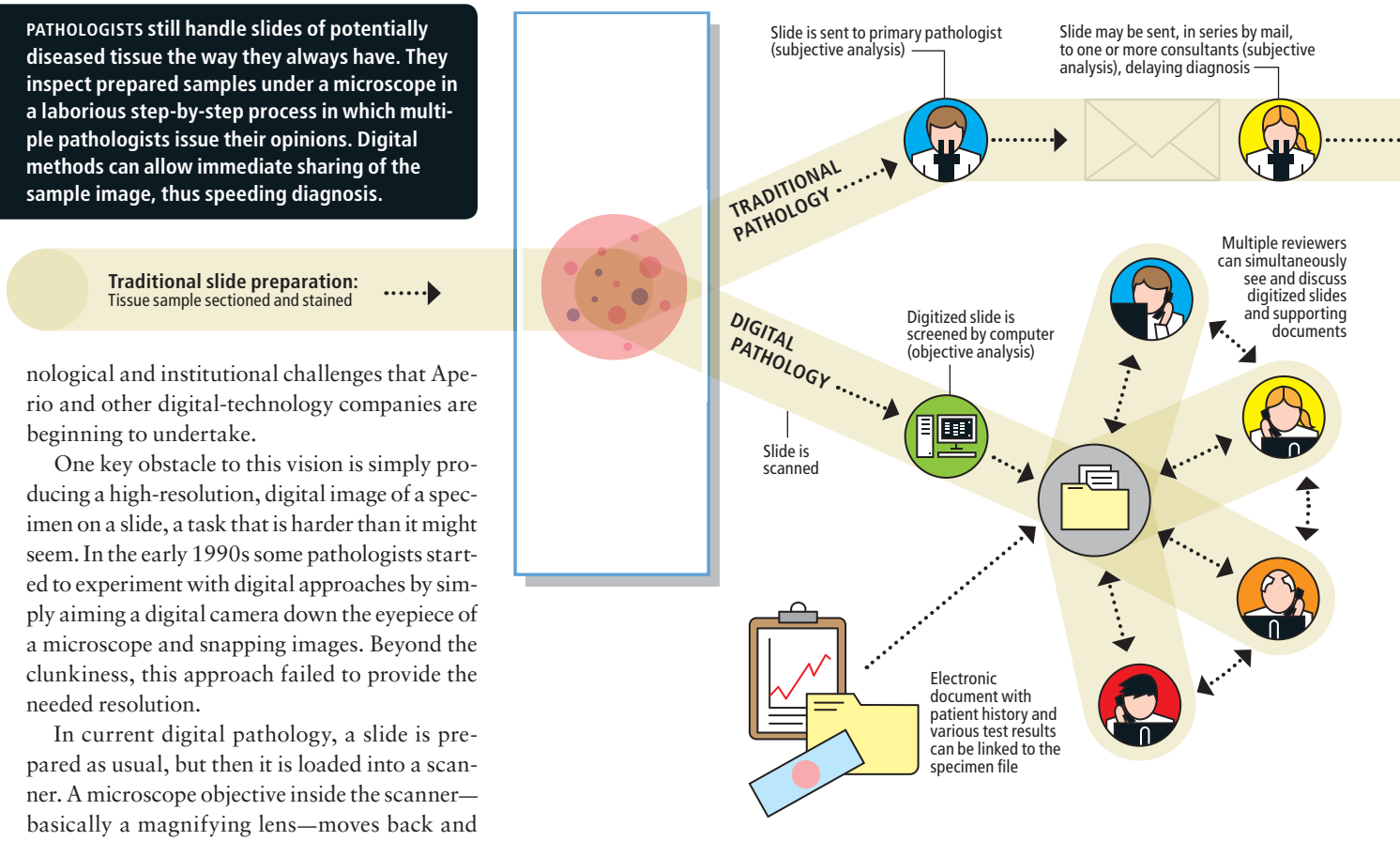
Turning to computers, though, will not take pathologists out of the picture. Instead digitizing slides can actually bring more pathologists into the process of making a diagnosis and thereby avoid medical error. Michalopoulos says that consulting with others on a diagnosis is "part of daily living in pathology." But today, he says, "you put a glass slide in the mail, and it takes two or three days—even with the fastest methods—to get there." With digital pathology, a tissue image could be sent electronically to others or, more likely, posted on a secure Web site and made available for a consultation with a pathologist on the other side of the world in just seconds. If consulting on a slide was that much easier, that much faster, pathologists might confer even more than they do already. As Michalopoulos says, "A consultation is the only way to resolve disputes, and experts often disagree. So you need to send slides to outside experts."

In combination, these two broad advances—more quantitative analysis and faster image sharing for consultation—serve as the main rationale for digitizing pathology samples. Getting there, though, will depend on solving a series of tech-

DIAGNOSIS MADE EASIER by the use of digitized slides of tissue samples will transform pathology, one of the few analytical professions to lag in adopting full-scale computerization.

QUICKHONEY

PATHOLOGISTS still handle slides of potentially diseased tissue the way they always have. They inspect prepared samples under a microscope in a laborious step-by-step process in which multiple pathologists issue their opinions. Digital methods can allow immediate sharing of the sample image, thus speeding diagnosis.



nological and institutional challenges that Aperio and other digital-technology companies are beginning to undertake.

One key obstacle to this vision is simply producing a high-resolution, digital image of a specimen on a slide, a task that is harder than it might seem. In the early 1990s some pathologists started to experiment with digital approaches by simply aiming a digital camera down the eyepiece of a microscope and snapping images. Beyond the clunkiness, this approach failed to provide the needed resolution.

In current digital pathology, a slide is prepared as usual, but then it is loaded into a scanner. A microscope objective inside the scanner—basically a magnifying lens—moves back and forth over the slide, and imaging technology, such as a CCD (charge-coupled device) camera, captures the image. Speed is of the essence in digital pathology. The scanner from Aperio, for example, can digitize a typical sample—about 15 millimeters on a side, or roughly the dimensions of a stamp—at a resolution of 0.5 micron per pixel, in about two minutes.

Those numbers reveal a fundamental challenge. Digitizing just one such slide to the resolution needed for detailed viewing requires 900 million pixels. By comparison, a photograph that is 4 × 5 inches and scanned at 300 dots per inch—a standard resolution for printing in a magazine—is composed of only 1.8 million pixels. So the digitized pathology slide requires 500 times more pixels. Digitizing the images faster requires faster electronics both to collect and to process the data. Some scanners acquire an image on a glass slide in square pieces, called tiles, and then software stitches them into a complete digital slide. Other devices, such as Aperio's, scan a slide in stripes, like a fax machine, and build the image on the fly.

No matter how fast a scanner operates, the speed is never enough. "We probably [prepare] 1.5 million glass slides a year, not counting specialty stains and so on," says Jonhan Ho, a skin pathologist at the University of Pittsburgh Medical Center. With a single scanner running at two minutes per slide, scanning slides for that one medical center for a year would take three million minutes—more than five years of scanning 24 hours a day, seven days a week.

Is Digital Good Enough?

The other looming question is whether pathologists looking at slides from Aperio and other companies on a computer screen can identify tissue abnormalities as well as they can when examining standard slides under a microscope. Drazen M. Jukic and some of his colleagues at the Pittsburgh medical center compared traditional pathology and digital techniques in an article in *Human Pathology* in 2006. For the most part, these pathologists found the digital files to be about as good as microscope slides in terms of enabling them to diagnose diseases by reviewing the images.

If digital pathology is only just as good as age-old methods, what could make it better? An ability to share slides easily is one answer. The Net Image Server, together with the OlyVIA viewer software from Olympus, for example,

MORE TO EXPLORE

Digital Pathology Image Analysis: Opportunities and Challenges. Anant Madabhushi in *Imaging in Medicine,* Vol. 1, No. 1, pages 7–10; October 2009. Available at **www.futuremedicine.com/doi/abs/10.2217/iim.09.9**

Digitizing Pathology. Jeffrey M. Perkel in *Bioscience Technology,* Vol. 34, No. 2, pages 8–12; February 23, 2010. Available at **www.biosciencetechnology.com/Articles/2010/02/Imaging-Digitizing-Pathology**

QUICK HONEY (*icons*); JEN CHRISTIANSEN (*infographic*)

works much like an ordinary Web page. Instead of sending digitized slides—which can be gigabytes and bigger in size (as much information as three compact discs could contain)—this software creates a repository of slides on a Web site or on a server.

When a pathologist clicks on a thumbnail, the Olympus software downloads enough of the image to fill a viewing box on the screen. It is a lot like looking up an address on Google Earth, where a user gets a viewing box's worth of a satellite image. The viewer can see more of the satellite image by simply clicking and dragging with a mouse. The same can be done with OlyVIA. If a pathologist sends only pieces of a big file, others can view the digitized tissue images over a digital subscriber line (DSL) or cable connection to the Internet.

Although electronic sharing will make it easier and faster for pathologists to consult with one another, that feature alone does not bring completely new capabilities to medicine. But computerized image analysis may bring about a more fundamental transformation. Aperio and others have developed analytical software and are working on making advanced versions.

In certain cases, such as inspecting breast cancer images, pathologists can already move into the digital era. For instance, roughly one quarter of breast cancers create abnormally high levels of a protein called human epidermal growth factor receptor 2, or HER2 for short. This protein can be revealed in samples of breast tissue by staining the protein so that it can be seen in a tissue slide.

Traditionally pathologists look at these slides for the intensity of staining and the number of cells that are colored. Visual estimates of the extent of staining (the intensity measurement) can be quite variable between pathologists. Digitization, combined with software that measures intensity in every pixel, quantifies intensity measurements, allowing analyses to become more uniform and dependable.

So far only technologies from Aperio and BioImagene in Sunnyvale, Calif., are cleared by the FDA for interpreting digital slides for HER2 levels on a computer monitor. Leaders of digital-pathology companies, though, hope that more endorsements are on the way and that the technology will continue to advance. "In the future, not even very far away," says Gene Cartwright, head of Omnyx, a Pittsburgh digital-pathology company, "the computer might show you things that your eye might not see." As an example, he imagines pathologists wanting to quantify many stains used on the same slide. "If there were five stains and you want to judge their intensity by eye, forget it," he explains. "You can't do it, but it's pretty easy for a computer to analyze the intensity of different colors."

Future Fixes

Although several companies offer software for the clinical environment, pathologists themselves must be enticed into using these systems. To help that along, developers are focusing on creating a "cockpit" for pathologists. A monitor could display the digital slides of a gross specimen removed during surgery, as well as a patient history and reports summarizing various other test results.

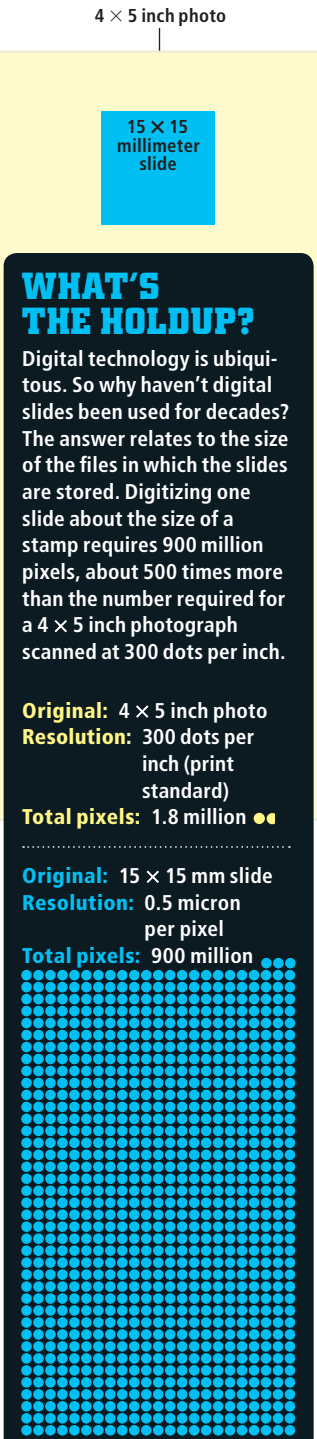
"That will take a number of years," Soenksen says. "You need to integrate the digital-slide information with a hospital's laboratory information system, with the radiology system, and other systems. You will need all of those interfaces to enable sharing." He adds, "Those interfaces are being established one at a time, and every interface is a custom development."

Despite the challenges, digital pathology is already coming to the clinic. But it is starting in niches, like the inspection of breast cancer markers. "A hospital might start by using digital pathology for 20 percent of its samples and then expanding that over several years," Cartwright says. "No one will go cold turkey in replacing conventional scopes."

And the issue of resisting change will always linger. "A pathologist feels at home with a microscope," Ho declares. "It's a tool, like a scalpel or stethoscope. It's an extension of our fingertips, and there's resistance to taking away the microscope."

Bit by bit, digital pathology will continue to work its way into clinical pathology—and expand, along the way, into forensics. Pathologists will interact more, quantify more, and develop increasingly objective ways to diagnose diseases and judge how well a treatment is working. ■

Mike May is a freelance science and technology writer who lives near Houston.



WHAT'S THE HOLDUP?

Digital technology is ubiquitous. So why haven't digital slides been used for decades? The answer relates to the size of the files in which the slides are stored. Digitizing one slide about the size of a stamp requires 900 million pixels, about 500 times more than the number required for a 4 × 5 inch photograph scanned at 300 dots per inch.

Original: 4 × 5 inch photo
Resolution: 300 dots per inch (print standard)
Total pixels: 1.8 million

Original: 15 × 15 mm slide
Resolution: 0.5 micron per pixel
Total pixels: 900 million