On a map, Palermo, Italy, on the island of Sicily, appears to be about 4,800 miles from Pittsburgh. To Anthony Jake Demetris, an MD professor of pathology and the Thomas E. Starzl Professor in Transplant Pathology in the School of Medicine and director of the Division of Transplantation Pathology at the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh, it’s as close as the nearest computer. Demetris is in the business of making the ocean between the cities irrelevant, at least to pathologists and patients in Palermo.

Demetris and other pathologists rarely see patients; rather, they see biopsies. Their professional worldview begins at a...
microscope. Yet the work they do is at the core of the practice of medicine. Masters of diagnosis, these men and women peer at glass slide after glass slide festooned with a slice of paraffin-preserved tissue. Is that cancer? About how many abnormal cells do I see? How much of biomarker X is in this sample?

What they decide guides treatment, and those decisions can determine whether a patient improves or declines. This traditional aim, figuring out just what’s going wrong in the body, is immutable. However, the ways in which anatomic pathologists practice their art and craft are changing, and Pitt’s own people have sparked many of these important transformations.

For more than a decade, the School of Medicine and UPMC have had a presence in Palermo in the form of ISMETT, a hospital that specializes in adult and pediatric abdominal and cardiothoracic medicine and surgery as well as multi-organ transplantation.

Of course, ISMETT has pathologists. But when the facility first opened, Demetris says, “They were getting ready to do organ transplants and biopsies. Now, we had trained pathologists over there, but it was just a few years’ training period. Our entire team felt better if there could be some sort of link between Pittsburgh and Palermo.”

There wasn’t a Pittsburgh/Palermo link at the time, but they created one and called it “telepathology.” In the beginning, telepathology was a valuable tool, albeit a primitive one. Not because of a lack of brainpower, but because of the limits of extant technology.

A patient in Palermo is about to undergo a biopsy. He’s prepped, the tissue is excised, a lab tech affixes the sample to a slide, and a pathologist in Pittsburgh is ready for a consult. But it’s pretty expensive, not to mention time-consuming, to fly a doc overseas …

“So,” says Demetris, “what we did was have a camera mounted to a microscope [in Palermo]. They’d take a snapshot and send it to us via e-mail.” The problem was that this picture was far from the big picture.

“The thing that’s inconvenient about it is twofold,” Demetris says. “One, you don’t have all the other information [in the patient’s chart] that goes along with it and, two—you know how you can move around a slide on a microscope?—well, working with snapshots, our view is limited to what the sender sends.”

Thus necessity became a mother for the nth time.

Demetris and colleagues crafted software that allowed docs in Palermo to paste several images, as well as patient data, into a message. This “store and forward” pathology was an improvement, sure, but not enough of one. Soon thereafter, the Pitt/Palermo team rigged a microscope at ISMETT with tiny motors and gears and, using readily available software, was able to manipulate the scope’s field of vision over the Internet.

“That’s actually old technology,” Demetris says of something just a few years into its life. “It became cumbersome. It took too long to review slides.” The work got done and got done well, he adds, but something faster was needed.

The team decided to scan and digitize such slides, taking thousands of pictures and quilting them together with software. The resulting mosaic represents an image of the entire sample that, thanks to the dizzying detail captured by the thousands of little images, can be manipulated so that a Pittsburgh pathologist can look at it from any perspective he chooses.

“It’s kind of like the technology used for...
Google Earth,” Demetris explains. “You find a city and then you zoom in on a house or something. It’s the same principle with a [digital] slide. The slides are put on a secure server, and you go to a Web site that contains the patient’s information and that image. You can go right in like you’re practicing pathology right in Palermo.”

So the biopsy is taken, a diagnosis of liver disease is made, transplantation is indicated, an organ match is found, and surgery is performed. And all of this with the Palermo patient probably unaware that a pathologist had any role in the process, let alone that the pathologist did his work in Pittsburgh.

In 2007, a 43-year-old woman—we’ll call her Rosa Costa—visited ISMETT after a nuclear magnetic resonance (NMR) test at another Italian hospital showed that there was a lesion on her liver. What kind of lesion, though, was unclear to her doctors and to the radiologist who examined her NMR scans.

At ISMETT, doctors went into the lesion with a needle to sample a portion of the tissue for a pathologist to examine. They hoped the resulting histology could provide some definitive answers.

Marta Minervini, an MD, was chief of pathology at ISMETT at the time. (She has since arrived in Pittsburgh to take a post as an assistant professor of pathology.) Minervini examined the slides, reviewed the images from radiology, and became pretty sure she was looking at an adenoma, which, she feared, had the potential to develop into malignant hepatocellular carcinoma. Such a cancer could kill a person in just a few months without surgery. But Minervini wasn’t certain what to conclude.

A surgical resection of the lesion would give an even clearer picture; but was it necessary? Clinicians, naturally, want as much certainty as possible before they decide whether to order surgery. Opening the body, no matter the skill of the surgeon, is always a risk (and costly).

“I didn’t have any other colleagues over there, but I wanted a second opinion,” Minervini recalls. “I was working alone and considered it a difficult case. That’s why I decided to post it, to send it to Pittsburgh for a second opinion.”

Minervini’s report—a narrative accompanied by histological and radiological images—noted that the lesion was fed by a number of aberrant arteries. Some findings are more compatible with hepatocellular adenoma [a potential malignancy], she wrote, while others are more suggestive of focal nodular hyperplasia [a kind of benign tumor]. Then she clicked “send.”

Less than 24 hours later, the response came from Demetris.

“I agree that the interpretation of this case is difficult,” he wrote. After suggesting further histological tests, Demetris came to this conclusion: “In the meantime, I would probably recommend that the liver be resected . . . .”

Given the very real risk of a malignancy, Costa’s clinicians decided to remove the lesion. “There was a reasonable conclusion that this
lesion had to be removed from the patient because it could be evolving into something worse,” Minervini says.

The practical benefits of the Pittsburgh/Palermo connection are obvious—readily available expertise from the other side of the world in real time. And telepathology can make a difference closer to home, as well. In a hospital system like UPMC’s, not every hospital necessarily has a pathologist from every subspecialty. Yet the long-term implications of this scanner technology are much, much larger.

“This,” says Demetris, “will revolutionize pathology. It’s already starting. With the help of engineers, and mathematicians, and software designers, you name it, we’re getting bigger and better, and I think someday the field would be better named ‘diagnostic medicine.’ We’re adding so much information to what we do.”

The one thing that pathologists have always been good at, Demetris says, is absorbing and interpreting tons of visual data. With education and training, he says, a good pathologist can quickly and accurately see patterns in slides. “But in terms of patient care,” he adds, “it sometimes irritates other specialists (such as a cardiologist or oncologist providing care), because they’ll say ‘This is only semiquantitative.’ We’ll say, 'There's a moderate amount of X, about 50 percent,' and they want to know if it’s 52.3 percent.”

When a lab worker scans a slide and hands over to the software developed here at Pitt, the pathologist’s interpretive skills are joined with the computer’s ability to quantify. And this arrangement, known as digital pathology, has broad implications for patients.

“We can now easily quantify the amount of a biomarker,” Demetris says. “In women who have breast cancer, an important predictor of outcome is the expression of estrogen and progesterone receptors. We have programs, they’re not quite mainstream, where you can stain the tissue and then [the program] will tell you how many cells or what percentage of cells are positive.”

On the phone from Boston, where he was giving a talk on telepathology, Demetris remarked, “The reason I’m here is that we were one of the earliest adopters of this technology. The images you get from whole-slide imaging aren’t as good as a microscope right now, but [the technology is] pretty darn close, and I think it will eventually surpass the microscope.”

As it happens, Pitt and UPMC, in partnership with GE Healthcare, are doing their level best to make sure this happens by December. A joint venture called OMNYX, with offices adjacent to PNC Park, is about to roll out software and digital scanners that will make packing and mailing glass slides between distant pathologists a thing of the past.

Anil Parwani, associate professor of pathology and director of the Division of Pathology Informatics, is one of several School of Medicine faculty members consulting with OMNYX.

While scanning and digitizing pathology slides isn’t a technology that’s only being pursued in Pittsburgh, Parwani, an MD/PhD, says that OMNYX is building a better—perhaps the best—digital pathology mousetrap.

“We’ve been scanning glass slides here for a long time; maybe five or six years now,” Parwani says. “When [GE] decided to partner with an institute, they chose us because of our experience and our understanding of this technology.”

OMNYX, Parwani says, manufactures scanners—at a plant in New Jersey—that are about five times faster than anything else out there. That’s great, he says, but what makes OMNYX likely to be a successful commercial venture is its software.

“The [software] is integrated with whatever computer system you already have in place, so you don’t have to go to several different systems to get all the information,” he says. “Everything, including all the patient information, is [right there], and being able to look at the image and this information simultaneously is a very positive thing.”

The 500-megabyte images OMNYX’s scanner captures can be manipulated in all manner of ways on the computer screen, just as glass slides can be manipulated under a microscope. A pathologist can zoom in, zoom out, and scroll over to another segment of the slide.

“We’ve built into the system a lot of things you can do with the image after it’s acquired,” Parwani says. “You can take pictures, you can measure things, you can run algorithms to quantify the intensity of a biomarker. All these things will enhance the pathologist’s workflow, making it more efficient, making it more robust.”

Most of this progress, Parwani says, has been made in the past two years, and the commercial launch of OMNYX’s products is nigh. The company recently showed off its wares at the College of American Pathology conference in Chicago. Pathology departments worldwide should be able to purchase both the OMNYX scanner and software by December.

Pathology is an interpretive specialty, so it’s quite possible for two pathologists to draw two different conclusions from the same slide. Today, though, pathologists are implementing quantitative tools and objective measures—to reduce the “interpretation gap.”

Traditionally, pathologists have reviewed their work after the fact at periodic departmental review sessions. At these meetings, a few cases are selected and discussed, and group members try to reach consensus on just what it is they’re seeing.

But if it turns out that, say, a population of cancer cells was missed or amyotrophic lateral sclerosis was misdiagnosed, the patient is already either being treated for a disease he doesn’t have or is not being treated for something that is afflicting him. Retrospective, blind reviews show that errors are made in as many as 6.7 percent of cases.

About two years ago, Parwani and others pilot tested a computer program they’d designed that allows for proactive quality-assurance reviews of pathology slides. About six months ago, it was implemented in all UPMC hospitals. It’s now commercially available and used throughout the country.

The system works like this: A pathologist has spent the day working on his cases. He’s seen the slides, reviewed the patient data, and made his report. As he goes to electronically file the case, suddenly, and at random, this message comes across his screen: “This case has been selected for quality assurance review.” He can’t enter the report into the system.

“At that point,” Parwani says, “the case will be removed from the work list and sent to a second pathologist who has been pre-assigned...
to look at all the quality-assurance cases. This pathologist will get the glass slides and the report and will write his comments in the computer system.” The system flags about 8 percent of each pathologist’s cases.

The quality-assurance pathologist then has 24 hours to review the case. If the two pathologists agree, great. If they don’t, they work together or with other colleagues to reach a consensus. Parwani is the senior author of a 2010 American Journal of Clinical Pathology paper on this system. In the paper, Parwani et al. report that minor disagreements (those with an academic interest to pathologists, but with no impact on patient care) were found in 2.2 percent of the reviewed cases and a mere .07 percent of cases resulted in a moderate disagreement (meaning the issue may be of some clinical importance but is highly unlikely to impact the patient).

Parwani thinks that the mere fact that a case may be flagged for review causes pathologists to pay even more attention to their work, reducing errors proactively. “The number of amended reports has decreased,” he says, since the quality-assurance system has been in place. “I think this is really improving the quality of our work.”

Thyroid cancer is relatively rare; there are about 40,000 new cases diagnosed annually in the United States. On the other hand, thyroid nodules, a possible indicator of thyroid cancer, are very common. “The question is,” Pitt pathologist Yuri Nikiforov says, “Is the nodule benign or malignant?”

At most hospitals, the first step in thyroid cancer diagnosis is removing a population of thyroid cells by needle and testing them in a cytology lab. “This is a very accurate test,” Nikiforov says, “but it has intrinsic limitations. It can only establish a conclusive diagnosis of whether [the nodule] is benign or malignant in about 70 percent of cases. In the remaining cases, cytologists have to say, ‘It’s indeterminate. That’s the best we can do.’”

There’s one way to hedge your bet here, and that’s to remove the thyroid lobe. Surgeons then send the excised lobe to a lab, where pathologists can make a definitive diagnosis after examining the tissue under a microscope.

If the pathologist determines the organ is cancer-free, that’s great, of course, but it’s not a free pass, as Pitt’s Marina Nikiforova explains: “There [can be] a lot of complications if a thyroid is removed. The patient will need hormonal therapy, and the surgery itself is not benign; it can have many post-surgical complications,” including nerve injury and a loss of voice.

Of course it’s not welcome news if the nodule is malignant, for obvious reasons. And
that unpleasant news can get worse. Once a malignancy is diagnosed from an excised thyroid lobe (there are two of them), a surgeon has to go back in and get the other one. And this second surgery can present many of the same complications as the first.

Yuri Nikiforov and Marina Nikiforova are husband and wife. He is an MD/PhD professor of pathology who leads the Division of Molecular Anatomic Pathology, and she is an MD associate professor of pathology. Each is a codirector of the Molecular Anatomic Pathology Laboratory.

The Nikiforovs continue to refine and improve a test they’ve developed that has taken much of the guesswork out of thyroid cancer diagnosis and led to the reduction of unnecessary surgery.

“Basically, what this test does is look for a panel of seven known mutations” that indicate malignancy, Nikiforov says. “We take all these indeterminate cytologies and split them into benign and malignant.”

Every thyroid patient at UPMC hospitals is given the test, and UPMC is the only hospital system in the country where it’s available to all. While the molecular test isn’t perfect—“The seven mutations we test for, they account for 75 percent of all thyroid cancers,” Yuri Nikiforov says—it does allow for treatment strategies.

Reading that 2008 MRI report, amid all the information on her osteoarthritis, Matute learned that she had a small nodule on the right lobe of her thyroid. “Even my physician didn’t see it at first,” she says. “It said, ‘Incidentally.’ It said, ‘Incidentally, there is a 2-centimeter nodule.’”

Although not a cause for panic, this is an “incidentally” that’s surely a cause for concern. Matute decided to go to UPMC Presbyterian for further tests—fine-needle aspiration (FNA) at first. Doctors would drive a needle into the nodule, excise some cells, and then test the cells to see if they were malignant or had a likelihood to become malignant. Yet, pathologists found, the doctors hadn’t extracted quite enough cells for a reliable cytology test. However, there were enough thyroid cells for the test developed by the Nikiforovs.

The test revealed mutations—enough to suggest that there was an 85 percent chance that Matute’s cells were malignant.

“I was given the option of going in for another FNA. But why should I have another needle stuck in my neck—it’s painful—if I don’t have to?” Matute says. “I decided to get surgery.”

Her thyroid was removed in May 2008, and the post-op examination found that the nodule indeed was malignant. She recovered well, without complications. Today, Matute says, she’s doing fine. So much so that she’s about to embark on a trip to China.

“This test saved me time, saved me pain, and got the cancer out,” she says.

Improving diagnosis, presenting targets for therapy, cutting costs, saving lives, and making the information necessary to do all that available in an instant and at just about any location. None of this makes pathologists any more visible to patients. And really, fundamentally, it doesn’t change the core of pathology; it adds to it.

“What is pathology? Well, it’s still a diagnostic specialty,” Yuri Nikiforov says. “But now it’s not only diagnostic, it’s providing treatment strategies.”

The Nikiforovs are practitioners of molecular pathology, a field that came into its own once the map of the human genome was first published in 2001. Having assembled the massive jigsaw puzzle that is the human genetic code, scientists went about tracing how mutations correlate with disease states.

The husband-and-wife pathologists spend a lot of time sifting through the human genome to find out why, among other things, certain cancers respond to treatment while others, which look the same under the microscope, do not.

This work has given them a unique perspective on the future of pathology and medicine.

“Pathology is where we make distinctive diagnoses,” Yuri Nikiforov says. “But when we distinguish certain types of cancer, we’ll say, ‘This is colon cancer,’ and treat it.” But not all colon cancers are created equal. “Yes, this is colon cancer,” he continues, “but there are different genes that these cancers possess and different drugs that act on different genes. We need to find out which cancers have which subabnormalities, and why these subabnormalities occur to let us better know how to treat this disease.”

“For sure, cancer is a genetic disease,” he continues. “It’s considered that multiple genetic abnormalities need to cumulatively occur in order for a cancer to develop, and in some cases, we know zero of these mutations.

“Take colon cancer,” he says. “‘Now we know of seven or eight mutations. Eventually, I think, we’ll find about 20.’ One person’s colon cancer could have eight of the 20 mutations, and another’s may have a different eight of the 20. Others still can and will have different combinations of all these possible mutations. Knowing what the mutations are provides a robust set of therapeutic targets.

“So we develop drugs to treat each of the individual 20,” Yuri Nikiforov says. “Then, depending on the combination of the mutations in a patient, we can find a very good combination of drugs. We’ll have a general group of therapies for this disease, but depending on the specific genetic makeup, we’ll be able to assemble a therapeutic regimen specific for the patient.”

But the true age of personalized medicine is not quite upon us, Yuri Nikiforov notes:

“When the human genome project was finished, everyone said, ‘In 10 years, we’ll have personalized medicine.’ That’s not going to happen. That was overly optimistic. But, it will happen. It’s only a matter of time and resources.”