Pay Attention to the Pathologist Behind the Curtain

"You have doctors you've never met, but who are absolutely essential to your care," says Kent B. Lewandrowski, MD, associate chief of Pathology and director of clinical services for the Pathology Department at Massachusetts General Hospital. "Pathologists are in the background, but are key to diagnosis, treatment and care."



ith the growing sophistication of pathology laboratory techniques and new knowledge about specific genes and molecules involved in cancer subtypes, pathology has become more important than ever. Accurate diagnosis can dramatically improve cancer care.

"Pathologists may work behind the scenes, like the 'man behind the curtain' in the *Wizard of Oz*," says David N. Louis, MD, pathologist-in-chief at Mass General. "But

until test results come back from the pathology lab, your doctor probably won't know your diagnosis or likely treatment for certain." Louis estimates that at least 70 percent of all hospital decisions are based on pathology lab results.

Mass General has a long history of excellence and innovation in pathology. Its pathologists were among the first to subspecialize surgical pathology into 13 different disciplines. Now there are pathologists who concentrate on diseases of the breast, the skin, or the lungs, for example. In its cutting-edge pathology labs, pathologists are applying the latest research findings about genetic abnormalities to create new diagnostic tests. They can match an individual cancer's genetic fingerprint to a specific targeted therapy.

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Telltale Shapes and Colors

Most people think "pathology" is what they see on TV shows like "CSI," where forensic pathologists determine cause of death. Pathologists at a hospital instead focus on tests and procedures that are key to disease diagnosis, treatment and management. "At Mass General, we do about 150,000 tissue-based analyses, which are largely to diagnose tumors, and about 10 million blood and urine laboratory tests and 70,000 blood product transfusions a year," explains Louis.

"CSI" has it right in one way. This is not your grandfather's

pathology, thanks to molecular diagnostics. In decades past, pathologists prepared slides of tissues and then stained different features purple and pink. The patterns of colors indicated something about the health of the cells.

Today, pathologists still look for patterns in shapes and colors, but at the molecular level. Slides are likely stained brown, green or red, and indicate the amount of a particular protein or marker in a cell, or whether a cell has activated a gene involved in cancer.

"We used to say: this slide has a flower-like pattern with

pink elongated cells or a polka dot pattern with huge malignantlooking purple cells," explains Louis. "Today we can say: these cells are expressing too much protein X and have a mutation in gene Y. These molecular features tell us more about the cancer than we could see before."

Researchers are identifying many mutations that have a role in causing cancers, providing targets for therapeutics. Oncologists are requesting diagnostic tests that show these mutations to help them select the best therapies for their patients. To create such tests and make them available to clinicians, Mass General has established the Diagnostic Molecular Pathology Laboratory and the Molecular Pathology Translational Research Lab.

Super Specialists

Surgical pathology is essentially the analysis of tissue samples obtained during a surgical procedure. At Mass General this specialty is further subdivided into 13 subspecialties. "For almost every organ system, we have a

specialty," says Louis. The result is extremely specific knowledge about what can go wrong in each organ system. "That's why we are the place where generalists look for a second opinion."

"We instituted subspecialization because pathologists must talk the same language and understand the same issues as the oncologists, surgeons and radiologists who specialize in those organ systems," explains Gregory Y. Lauwers, MD, director of Surgical Pathology and director of Gastrointestinal Pathology at Mass General. "It also improves clinical care." Specialized surgical pathologists can help clinicians better understand tumor types and how they may behave. They are integral to the multidisciplinary teams who work together to produce the most precise diagnosis and treatment for each patient. (continued on page 8) PATHOLOGIST BEHIND THE CURTAIN (continued from page 7)



Karen E. Chelcun Schreiber

This expertise attracts people with rare and hard-todiagnose cancers to Mass General. Karen E. Chelcun Schreiber, a Wisconsin resident, began to research gastric cancer after her older brother was diagnosed with advanced gastric cancer at age 56. She discovered that her family was affected by an unusual disease — an inheritable gastric cancer seen in only 100 families worldwide. Her mother had died of gastric cancer at age 52, just six months after diagnosis. Genetic tests determined that Chelcun Schreiber's brother carries the Hereditary Diffuse Gastric Cancer (HDGC) gene as does she. That meant that she too would almost certainly develop this cancer.

When she came to Mass General in 2008 for a procedure to scope her stomach for cancerous or precancerous lesions, she specifically asked which pathologist would be examining her tissue. After learning it was Lauwers, she asked to meet with him. She knew the critical role of the pathologist, who must examine hundreds of slides of the stomach to look for lesions.

Many patients who learn they carry a high cancer risk opt for more extensive preventive screening to detect the cancer early, at a treatable stage. But familial gastric cancer patients have fewer options. Instead of causing localized tumors, HDGC spawns stealth tumors that infiltrate the lining of the stomach and evade detection on CT scans until an advanced stage. That's why at age 50, Karen Chelcun Schreiber decided to have her entire stomach removed, before any tumor cells present could metastasize to other organs.

Because of the disease's rarity, few cancer centers have performed even one of these prophylactic procedures, but surgical oncologist Sam S. Yoon, MD at the Cancer Center has now done eight such cases, making the Cancer Center's series one of the largest in the US.

"I came to Mass General because Dr. Yoon had the specific expertise I was looking for, combined with an excellent track record and a commitment to patient care," Chelcun Shcreiber says. "My stomach was literally in the best hands possible, with Dr. Yoon in the OR and Dr. Lauwers in the path lab."

Classifying Malignancies

Another major area of pathology, hematopathology, deals with the study of blood and lymphatic fluids, and also biopsies and smears of bone marrow and lymphoid tissues. There are more than 40 different malignancies of the blood, bone marrow and lymphatic systems.

"Classification is the language of medicine," says Nancy Lee Harris, MD, director of Hematopathology. "We must define diseases, name them, and diagnose them before we understand their biology and effectively treat them."

Previously, pathologists used several different classification systems for lymphomas, and this created confusion. In 1994, Harris and an international group of colleagues published a consensus classification system that became the most highly cited article of clinical medicine in that decade. It is now called the World Health Organization Classification and is universally used.

To make the correct diagnosis and determine the right treatment, hematopathologists use a variety of tests. They analyze morphology, enzymes and immune molecules, and use genetic techniques to identify antigen receptor genes and other genetic abnormalities. These tests enhance pathologists' ability to classify the many cancer subtypes.

For example, mantle cell lymphoma (MCL) is an aggressive disease requiring aggressive treatment. But under the microscope, its cells appear similar to the slower-growing chronic lymphocytic leukemia (CLL). MCL often used to be misdiagnosed, with disastrous results for patients.

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That changed after Andrew Arnold, MD, then at Mass General, identified a gene associated with the specific chromosomal translocation found in MCL. Harris and her colleagues at Mass General found that the protein produced by the gene (cyclin D1) was a specific marker for MCL. A test for that marker has become the gold standard and has greatly improved the accuracy of MCL diagnosis.

Finding the Needle in the Haystack

Cytopathology, an area of cancer pathology, analyzes single cells rather than tissues. The best known is the Pap test that detects cervical cancer. Because Pap tests are so common, a misperception exists that the practice of cytopathology is automatic and easy. In fact it is quite complicated and difficult. It involves checking tens of thousands of cells in a sample for very subtle, abnormal features in cell size, density of the cell's nucleus, and changes in the structures within the nucleus.

Detecting these features is like looking from an airplane down at the Patriot's football stadium parking lot to find particular bumper stickers that occur in one out of 60,000 moving cars. "It's technically feasible, and we do find the vast majority of abnormal cells," says David C. Wilbur, director of Cytopathology. "But it is very daunting, like looking for the needle in the haystack."

New image analysis software developed in Wilbur's Cytopathology Unit has improved the detection of abnormalities by flagging suspicious areas in cells. "We use a variety of instruments and molecular techniques to help us maximize the accuracy of screening for cervical cancer and its precursors," Wilbur says. The Cytopathology Unit is conducting clinical trials of nextgeneration automated screening devices and molecular techniques, and developing guidelines for using such techniques.

Less-Invasive Techniques

Another pathology innovation at Mass General that benefits cancer patients is fine needle aspiration, which often replaces surgical biopsy for diagnosis. Pathologists guide a thin needle to the targeted tissue and withdraw cells for analysis. This less traumatic, non-scarring procedure is particularly important for thyroid and lymph node biopsies. It can also extract cells from deep organs in the body.

"If you have a lump somewhere, doctors at Mass General may be able to go in with a needle, aspirate cells, and make a diagnosis without needing more invasive procedures," says Lewandrowski.

Pathologists play a key role in a cancer patient's journey from diagnosis through treatment. They may work behind the curtain, but patient lives are very much in their capable hands too. **•** *- Cathyn Delude*

Simultaneous analysis of three genes (HER2, EGFR, and cMET) in esophageal cancer cells. Each dot represents a single gene copy, with green dots corresponding to HER2, red to cMET and white to EGFR. Each blue nucleus contains between two and four copies of each gene. Analyzing all three simultaneously allows the rapid screening of patient tumor samples for genetic changes that could direct drug therapy.

The Hunt for Mutated Molecules

Treatment decisions often hinge on the results of diagnostic tests. The challenge that comes with the rapid-pace discoveries of cancer-causing genetic mutations is to develop new molecular diagnostics to find them.

In 2006, studies showed that colon cancer tumors that develop a certain genetic mutation, called Kras, do not respond to the new anti-cancer drug Erbitux. Last summer, the American Society of Clinical Oncology recommended that all colon cancer tumors be screened for Kras before doctors prescribe the drug, since it would not benefit patients with Kras.

"Overnight, oncologists started asking pathologists for this test because it helps them with their decision tree of whether to put a patient first on Eribitux or a different drug," comments A. John lafrate, MD, PhD, director of Diagnostic Molecular Pathology Laboratory at Massachusetts General Hospital.

Doctors already use genetic tests to screen breast cancer tumors for a genetic anomaly that makes them responsive to the drug Herceptin. Likewise, Gleevec attacks a specific mutation in chronic myelogenous leukemia. Now before prescribing such drugs, doctors do the genetic tests.

That's a problem for newly discovered mutations, however, since it takes time and effort to ensure that tests for them are accurate and reliable.

For example, in 2004, Daniel A. Haber, MD, PhD, director of Massachusetts General Hospital Cancer Center, discovered that a mutation in a growth factor cell receptor, EGFR, exists in about 10 percent of non-small cell lung cancers. If patients have that EGFR mutation, they respond to the drug Iressa.

"That's great to know," says David N. Louis, MD, pathologist-inchief at Mass General. "But we need a diagnostic test that can identify those patients in a reliable way, and tell us not with 20 percent certainty but beyond a shadow of a doubt."



Developing such tests is the province of lafrate's **Diagnostic Molecular** Pathology Laboratory. The laboratory has now developed a diagnostic test for EGFR and is working on tests for other mutations. These tests will guide clinical decisions and help doctors pick the best therapy for individual patients. - Cathryn Delude