Peter Byers, M.D., has a message for his fellow physicians: precision medicine is coming. “It’s going to challenge you, it’s going to excite you, it’s going to bring you into a new world of medicine, and it’s going to give you a different understanding of the families that you work with,” he says. Byers, a UW professor in the Department of Pathology and the Division of Medical Genetics, is the director of UW Medicine’s new Center for Precision Diagnostics.

Traditional medical research and care is predicated on testing many people and coming up with a one-size-fits-all treatment. But one size rarely fits all. Precision medicine takes a different tack: the more we know about an individual, and the better we understand how a disease or a condition manifests in that individual, the better we can tailor their medical care.

What makes the coming wave of precision medicine possible? It’s a term used by cancer innovator and UW Medicine faculty Tony Blau: the “omics.” Genomics, proteomics, metabolomics, transcriptomics. All tools that allow researchers to understand how a patient’s body works at a molecular level.

Arguably, genomics is in the vanguard; advances in gene sequencing technology made over the past 10 years make a great deal of precision medicine work possible. But Bob Waterston, M.D., Ph.D., the William H. Gates III Endowed Chair in Biomedical Sciences and one of the founders of The Human Genome Project, notes that genomics will partner closely with the other omics.

“Transcriptomics, proteomics and metabolomics are all measuring, in one way or another, the output of the genome as it reacts to its environment,” says Waterston. “These measures can provide useful readouts of the current status not only of genetic diseases [such as cancer], but other diseases as well, like diabetes, autoimmune diseases and cardiovascular diseases.”

Byers has high hopes for the Center for Precision Diagnostics, created to usher in this new type of care at UW Medicine. In addition to educating faculty, students, trainees and staff about precision medicine — and in addition to using exome technology to examine patients’ tissue samples — he intends the center to serve as a transformative resource for physicians in Seattle and throughout the region.

“With precision medicine, patients and families and doctors will form a cooperative relationship,” Byers says. “The nature of healthcare will change.”

Read about UW Medicine’s use of precision medicine technology — related to breast cancer, eye disease and Alzheimer’s disease — on the next few pages.
“Back then, cancer seemed like such an incredibly difficult, intractable problem,” says Tony Blau, M.D., Fel. ’94, director of the UW Medicine Center for Cancer Innovation.

Blau knew how tough cancer was to beat, having done an oncology fellowship involving leukemia patients in 1989. “You threw as much radiation and chemotherapy as you could get away with at a cancer patient, gave them as much as they could possibly take, and then rescued them with someone else’s bone marrow,” Blau says. It was the best care available, and it didn’t always work.

Although Blau did not pursue cancer research immediately after his training, he grew interested in the topic again about five years ago, when gene-related medical technologies started to improve exponentially. At the same time, he started to attend conferences with his wife, oncologist Sibel Blau, M.D. The huge distance between the technologies available to researchers and the tools available to oncologists left a strong impression on him.

“It struck me that the approach we’re taking to cancer needed to be fundamentally restructured,” says Blau.

Restructuring cancer care

Blau’s plan can be seen at work in the Center for Cancer Innovation’s triple-negative breast cancer trial. It sounds simple enough: putting the patient at the core of the experiment. “The idea is to leave no gap between what a research lab can offer and what’s made available to our patients,” says Blau. The other primary idea: to work with just a few patients — at least at first — to gain as much data as possible about the evolution of their tumors.

Helping Blau in this initial trial is a group of women with metastatic triple-negative breast cancer, including Cathleen Olivas, a 57-year-old woman from Auburn, Wash. First diagnosed with breast cancer in 2007, Olivas had one breast removed, then the other. Then the cancer came back in March 2013.

When Sibel Blau asked Olivas to participate in the trial, her response was immediate, unwavering and positive. “I didn’t even have to think about it,” says Olivas.

After Olivas and other patients have their tumors biopsied, the tissue is turned over to UW Medicine faculty to work with just a few patients — at least at first — to gain as much data as possible about the evolution of their tumors.

“The approach we’re taking to cancer needed to be fundamentally restructured.”
— Tony Blau, M.D., Fel. ’94
for whole-exome sequencing, RNA sequencing and the UW-OncoPlex™ panel, among other tests. Then, when possible, tumor cells are sent to the Quellos High-throughput Screening Core, where Tim Martins, Ph.D. (see page 16) investigates how the patient’s tumor responds to roughly 180 compounds. If there’s a “hit” — if a compound damages the tumor — Blau will try to incorporate the compound in the patient’s treatment, a process that, for investigational drugs, may involve the FDA and the drug company that produced the substance.

This is precision medicine at its most precise and responsive. And if the tumor grows resistant to the drug, the process is repeated: biopsy, sequencing, high-throughput screening, alteration of treatment.

All for one, and one for all

In describing his project, Blau often uses the phrase “all for one, and one for all.” He’s referring to bringing the best he and his colleagues can offer to a single patient.

He’s also referring to the sacrifices that the cancer patients — between 10 and 20 women for this initial trial — are making. Time, energy, tissue: patients give all of these to pursue knowledge and therapies not guaranteed to benefit them.

“For me, I honestly don’t know if it will accomplish anything,” says Olivas. “I’m fine with that. What they’re learning is amazing.”

And Blau and his colleagues are certainly going to be learning. They’re collecting enormous amounts of data. If this project works as Blau thinks it will, amassing information that helps deepen understanding of tumor evolution and potential therapies, he hopes to conduct a larger clinical trial for patients with any type of advanced cancer.

Today, however, he’s focusing on recruiting the patients he calls his heroes — women with metastatic triple-negative breast cancer. “Having their individual illnesses inform the world about how cancer works is a huge contribution to humanity,” Blau says.
Tim Martins, Ph.D. ’84, and James Annis work amidst the whirring and clacking of high-tech machines — machines that are changing medical experimentation at UW Medicine.

When Martins was in graduate school in the 1980s, the landscape was quite different. Researchers would conduct experiments in test tubes; then they moved on 8 x 12 plates — 96 wells in which to manually distribute materials like cells, reagents and compounds, and see how they would react with one another. Today, with plates containing 1,536 compartments and automated dispensers capable of filling each compartment with as little as 50 nanolitres, the game has changed.

“We’re able to do many experiments very, very quickly and reproducibly,” says Martins, director and principal scientist of the research core facility.

Testing compounds to fight illnesses

Martins and Annis divide the work at the Quellos High-throughput Screening Core. Martins handles the screening: using the 120,000 compounds in the core’s library to help scientists determine which ones might work to defeat a disease. Some of these substances are FDA-approved drugs; others may be in the testing stage; still others may be future candidates for testing. After diseased cell samples are exposed to the compounds, Martins can determine the compounds’ usefulness in damaging or killing the cells.

UW Medicine cancer researcher Pam Becker, M.D., Ph.D., has used the core to test compounds on cells donated by several of her patients, who have acute myeloid leukemia. For her project, Martins used these compounds at various concentrations to determine appropriate potency levels. “In just about every case, [high-throughput screening] has suggested an alternative treatment that would not have been next in line,” says Martins. “And from what I understand, it appears to be working very well.” (Read more about Becker’s work at uwmedmagazine.org.)

Following the genetic path to disease

James Annis, research scientist, is using the core’s equipment to study functional genomics: how genes, mutated genes and their products begin a process that can lead to disease — or to disease resistance. By combining the use of small inhibitory RNA molecules or siRNAs within screening paradigms, Annis can knock out a gene, track what happens afterward, and understand the intracellular pathways that are involved in the process. Martins calls this a truly powerful part of genomics.

“Just knowing a gene is knocked out...doesn’t link you to how a cell has responded downstream. The mutation may be over here” — Martins stretches out his arms to show the hypothetical distance — “but way over here is where the cell’s response is.”

Keeping discoveries in the region

The core, housed at the Institute for Stem Cell and Regenerative Medicine (ISCRM), has been in operation for approximately five years, conducting hundreds of projects and producing volumes of data for UW Medicine researchers and other organizations. The inspiration of ISCRM’s director, Randall Moon, M.D., Ph.D., the core was funded by a generous donation from the Quellos Group, LLC, and began offering research services with the addition of Martins, Annis and
When does the gray matter that resides in your skull resemble an aching knee or elbow? When Tom Montine, M.D., Ph.D., chair of the Department of Pathology and the Nancy and Buster Alvord Endowed Chair in Neuropathology, makes an analogy to explain the development of Alzheimer’s disease.

“In some respects, Alzheimer’s disease is like arthritis of the brain,” he says. Take a damaged joint; in responding to the injury, the immune system may inflict additional damage that later leads to arthritis. Similarly, Montine thinks the immune system may also speed Alzheimer’s disease in some patients. Recent genetic indicators point strongly to immune regulation in the brain as a key element of Alzheimer’s disease.

“What Montine and his colleagues are working toward, however, is to amass all the genetic drivers for Alzheimer’s disease, not just the genes that code for immune response regulators. They want a complete picture — the genetic architecture of Alzheimer’s disease. With genomic technology, he says, this is coming quickly. But just knowing the drivers isn’t enough.

“Genetics defines molecular relevance,” he says, “but it doesn’t define molecular mechanisms.” Montine and his colleagues need better experimental models that allow scientists to track the pathways — from their genetic origins to their functional effects — responsible for Alzheimer’s disease and other neurodegenerative conditions, such as Parkinson’s.

Precision medicine tools like genomics (to assess risk) and proteomics (to measure biomarkers that indicate the possibility or presence of disease) are helping scientists track the pathways and the drivers in Alzheimer’s disease. And once the pathways and drivers are better understood, Montine says, “we have a rational approach to therapeutic development.” A precision medicine approach, one tailored to specific forms of diseases in specific people.
"It’s sort of like having the sword of Damocles above your head," says Jennifer Chao, Ph.D., M.D., UW assistant professor in the Department of Ophthalmology. She’s referring to the diagnosis of macular degeneration, a condition that affects the sight of approximately 1.8 million people in the U.S., especially older people. There is no cure. “You go to the eye doctor, and you try to manage your symptoms, and sometimes there’s just nothing you can do,” Chao says.

Through a study being conducted at UW Medicine, however, Chao hopes to take several steps toward a cure, or at least toward understanding the causes of macular degeneration. And she has found a way around her first obstacle. How do you study a live, malfunctioning human eye — one still very much attached to its owner?

The answer is to create a partial model of the eye. To this end, Chao and her colleagues have recruited 12 volunteers. Some have macular degeneration, and some do not, but all of them donated blood.

First, Chao and her colleagues manipulated the blood cells to create patient-specific stem cells, which can transform into other types of cells. Then they prodded the stem cells into transforming into retinal pigment epithelium (RPE) cells. RPE cells maintain the retinal environment in the eye, and researchers think they’re connected to macular degeneration.

These clumps of RPE cells, which serve as models of the eye, are then tested at the Quellos High-throughput Screening Core — a service that enables rapid studies. They are first bombarded with factors thought to cause macular degeneration — factors that can cause cell death — and then exposed to nearly 2,000 medical compounds. The object of the experiment is twofold: to see if any of the compounds can save the eye models from dying and to better understand how macular degeneration affects the RPE.

The work has started, and rapid screening has shown some preliminary “hits” — therapeutic compounds that may work to defeat macular degeneration in one or more of the models. This is precision medicine in action — at a very early stage in the scientific process.

“It’s very exciting,” says Chao. She pauses when asked about the value of having the Quellos Core at UW Medicine. “I don’t really know where else we would do this,” she says. “It’s fantastic.”

See the story on the Quellos Core on page 16.

More at uwmedmagazine.org