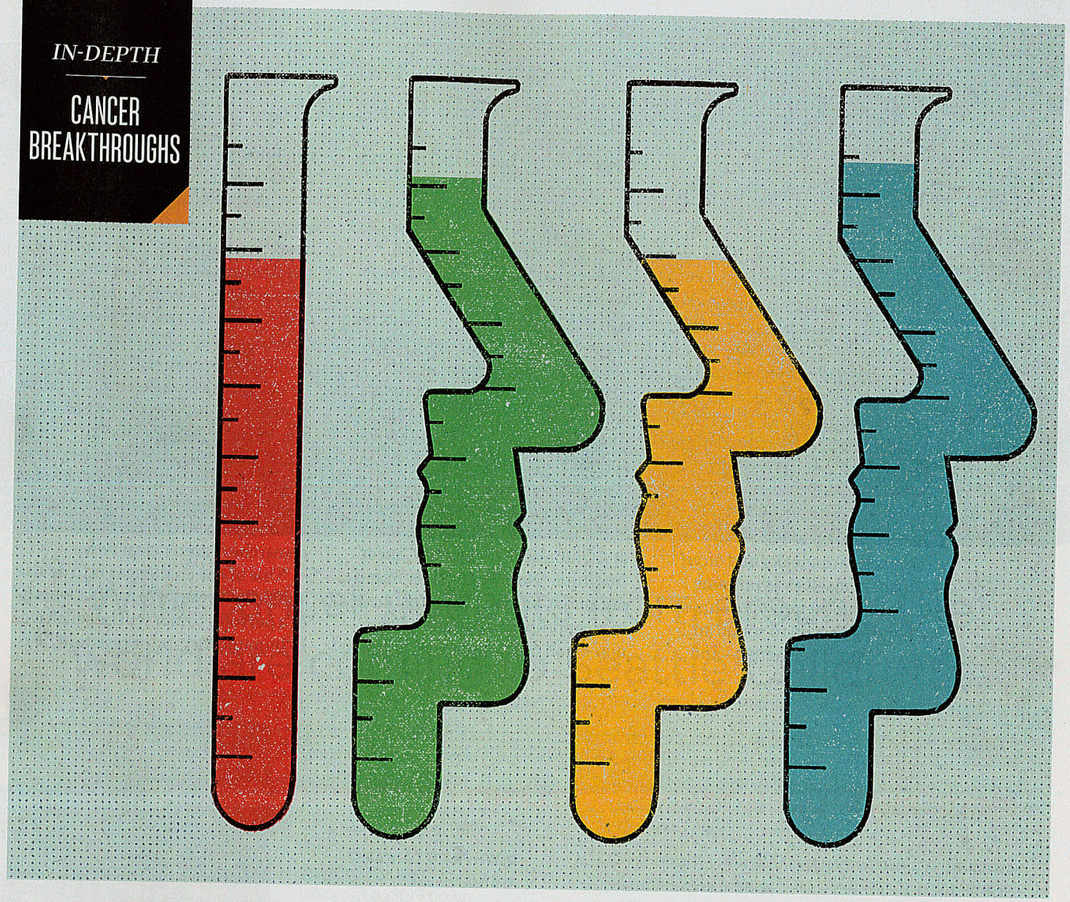

Tailor-made Cancer Care

How scientists are harnessing the power of knowledge and numbers to pinpoint the best plan of attack for individual cancer patients. BY AMY PATUREL

In the United States, nearly 600,000 people die from cancer each year. But what if doctors could help patients better navigate the disease—or circumvent it altogether—by better tailoring and more accurately recruiting different disciplines to battle the behemoth with information-based approaches?

"There has been a huge paradigm shift in cancer care," says Ramesh Rengan, M.D., professor of radiation oncology at the University of Washington School of Medicine and medical director of the Seattle Cancer Care Alliance Proton Therapy Center. "Historically, doctors believed bigger surgeries, more radiation and more aggressive chemotherapy regimens reduced the chance of recurrence. Now we understand that a multipronged, targeted approach leads to better outcomes for patients—even when it comes to the deadliest cancers."

In this information-driven space, engineers work alongside oncologists. Computer science masterminds collaborate with laboratory scientists. And researchers from all over the world have access to the same data and analytic tools to bring effective therapies to patients' bedsides more quickly. So instead of going at cancer harder, doctors are hitting it smarter.

ILLUSTRATION BY DAN PAGE

TARGETED TREATMENTS

The challenge in cancer therapy is to kill the cancer—with a scalpel, drug or radiation—while preserving healthy tissue. Minimizing damage to healthy tissues plays a critical role in patients' ability to battle the disease and to withstand other treatments should they become necessary. The goal: "For doctors to get in, do their job and get out," says Rengan. "In that way, we should approach cancer care like it's a national park—there should be no footprint that we were there."

Immunotherapy

Cancer cells are sneaky and often disguise themselves as immune cells. Immunotherapy acts almost as a homing beacon to sound an alarm—"cancer cell here!"—and unleash the patient's own immune system to battle the disease.

While the technology has been in doctors' arsenal for decades, FDA approval of immunotherapy for cancer treatment is still relatively new. But the results have been impressive, with researchers reporting unprecedented responses in melanoma, lung and kidney cancers.

"Data is coming out every few months showing that immunotherapy improves progression-free survival more than traditional therapies," says Edward S. Kim, M.D., chair of solid tumor oncology and investigational therapeutics at Atrium Health's Levine Cancer Institute. "Now we consider immunotherapy as a first-line treatment in all appropriate patients with non-small cell lung cancer, either in combination with chemotherapy or on its own."

The FDA has approved six immune checkpoint inhibitors for cancer treatment. And according to the Cancer Research Institute, more than 2,000 cancer immunotherapy drugs are in the research and development pipeline. But for all of its promise, there are still concerns. Releasing the brakes on the immune system could cause it to careen out of control and attack the skin, lungs, intestines, joints and other healthy organs and tissues. Plus, checkpoint inhibitor drugs only work for 20 to 30 percent of patients—and researchers aren't clear why.

"One of the challenges is to devise simple tests that will predict whether a person's tumor will be sensitive to immunotherapy or resistant," ex-

SMALL PHARMA, BIG PAYOFF: SPOTLIGHT ON MOLECULIN

After nearly 15 years as founder, chair and CEO of a publicly traded, multinational consumer products company called Drypers, Walter Klemp dipped his toes into life sciences in 2007. His company, Moleculin, went public in 2016 and it's already making a splash in the rare-cancer space. Klemp discusses why he decided to pursue drug development and how novel therapies are changing the way scientists think about battling cancer.

Q: WHICH EFFORTS ARE YOU MOST EXCITED ABOUT?
A: We're in clinical trials right now with a drug called Annamycin, which we believe has the potential to double the number of patients with acute myeloid leukemia who are eligible to receive a curative bone marrow transplant. If we're right, and we prove this in the clinic, we could save 10 lives each day in the United States.

Q: HOW DOES ANNAMYCIN WORK?
A: If you have AML and you get a bone marrow transplant, you have about an 80 percent chance of beating your disease [but] you've only got about a 20 to 25 percent chance of getting to that bone marrow transplant because the current induction therapies that make you eligible for the procedure are largely ineffective. That's where Annamycin comes in. We are hoping to demonstrate in clinical trials that it can provide a safer and more effective induction therapy.

Q: WHY RARE CANCERS?
A: There's huge moral benefit in targeting these diseases, but the economics of rare drug development are also compelling. Congress passed legislation that incentivizes companies that develop new drugs to treat a rare disease, including a seven-year period of market exclusivity. To sweeten the deal, they afforded accelerated approval pathways to companies who are going after rare diseases that also have a significant unmet need.

Q: HOW ARE MOLECULIN'S APPROACHES TO RARE CANCERS DIFFERENT?
A: The existing approaches in the rare-cancer space are largely inadequate or ineffective. There has been a lot of focus on targeted therapies and immunotherapy, but our approaches are radically different and they include three distinctly different tools: Annamycin, which shuts down the DNA of high-proliferating cells (like cancer); our 1066 portfolio, which has shown the potential to block the signaling functions that allow tumors to form and progress; and 1122, whih focuses on the metabolism of tumors and shuts off their fuel supply. The end result: Tumor cells starve and die. This multipronged approach allows us to play with combinations. If you have a rare, deadly disease such as glioblastoma or pancreatic cancer, we can throw everything we have at the disease simultaneously.

plains William Cance, M.D., deputy director of The University of Arizona Cancer Center. "Scientists are also paying attention to something called the tumor microenvironment, which is the area immediately around the tumor." In some tumors, the normal immune cells that live in this microenvironment act as a wall, preventing the immune system's T cells from reaching the tumor. Before the immune cells can attack the cancer, researchers have to find a way to break it down.

Proton Therapy

The radiation oncologist's goal is to hit a malignant tumor with the prescribed dose of radiation while limiting damage to surrounding tissue. Unlike photon radiation, which travels through and beyond the treatment site, proton therapy allows doctors to control, with precision, where the tiny proton particles release their energy.

"THERE HAS BEEN A HUGE PARADIGM SHIFT IN CANCER CARE. . . . NOW WE UNDERSTAND THAT A MULTIPRONGED, TARGETED APPROACH LEADS TO BETTER OUTCOMES FOR PATIENTS—EVEN WHEN IT COMES TO THE DEADLIEST CANCERS."

—RAMESH RENGAN, M.D., MEDICAL DIRECTOR OF THE SEATTLE CANCER CARE ALLIANCE PROTON THERAPY CENTER

The latest form of proton therapy, called pencil beam scanning (or intensity modulated proton therapy), releases a high dose of radiation that conforms to the size and shape of the tumor.

"The difference between pencil beam approaches and conventional proton therapy is like the difference between a laser and a flashlight," explains Thomas E. Merchant, D.O., Ph.D., chair of the radiation oncology department at St. Jude Children's Research Hospital. "The laserlike form is a narrow beam that can be turned on and off."

So instead of using a large beam, radiation oncologists deposit the dose layer by layer according to the contour of the tumor. Since each tumor requires hundreds or thousands of spots of radiation and beam position has to be perfect, proton therapy draws upon physics, engineering and mathematics.

Science is still trying to build the case that proton therapy is better than traditional radiation. As a result, proton therapy isn't always covered by insurance—and it's expensive. But according to Merchant, when administered correctly, proton therapy does ensure that the dose is delivered to the target.

Gene-Based Solutions

Whole genome sequencing is unlocking the door for scientists to discover novel treatments. Researchers are becoming more adept at identifying mutations and variants, and the technology is becoming less expensive. So instead of using chemotherapy to annihilate fast-growing cells indiscriminately, they're using gene sequencing to develop personalized treatments for patients.

"We're learning which gene mutations are driving cancer and identifying drugs that suppress them," explains St. Jude researcher Jinghui Zhang, Ph.D. "In breast and ovarian cancer, for example, mutations in BRCA1 and BRCA2 help doctors determine which treatment will be most effective." In some cases, drugs such as Tamoxifen and Raloxifene can even help prevent cancer from developing.

There's also a movement toward growing tumors outside of the patient using a patient's biopsy tissue. "Doctors grow these three-dimensional organoids in the lab using a medium that mimics the environment in the body, sequence them to identify appropriate treatments and eventually test drugs on that 3-D tumor," explains Allyson Ocean, M.D., associate professor of clinical medicine at Weill Cornell Medical College.

MATHEMATICS

Advances in artificial intelligence are enabling researchers to analyze mammoth data sets and develop algorithms to learn whether relationships and patterns make a difference in diagnosing cancer.

"Historically, AI models required researchers to program every eventuality and possibility into the algorithm itself, but this created a lot of complexity," says Roberto Novoa, M.D., a Stanford University dermatologist and clinical assistant professor. "One of the big advantages of deep learning is that the computers do it themselves."

Using image banks composed of thousands of benign and malignant lesions, Novoa and his team created a database of nearly 130,000 skin disease images and trained their algorithm to spot potential cancers. From the very first test, the algorithm was remarkably accurate. Its ability to correctly identify the most common and deadliest skin cancers was on par with that of 21 board-certified dermatologists.

Genomic Data Decoded

The goal of supercomputing and AI is to outsmart human beings not only in identifying cancer, but in guiding decisions about care. In this way, AI can be a powerful source of decision support for physicians scattered across the country.

In recent years, genetic scientists have uncovered hundreds of thousands of variants in genetic sequencing. These "variants of uncertain significance" may be harmless. However, if genetic testing

identifies a variant that is disease-causing, doctors can intervene. But when you have a huge population of harmless VUS, how do you detect the small subset that requires medical management? In 2015, The American College of Medical Genetics and Genomics established a framework of 28 criteria for interpreting genetic test results. The problem: The classification framework is completely qualitative, without any kind of scale to weight and rate the rules.

Sean Tavtigian, Ph.D., cancer researcher at Huntsman Cancer Institute, wondered whether a mathematical tool could validate the rules by mobilizing a handful of different data sources toward variant classification.

Using a centuries-old equation called Bayes' theorem, Tavtigian and his colleagues developed a computational tool that combines the different data sources and comes up with a probability for the final result with astonishing accuracy. With this tool, scientists can use data better and faster. And when you have a high genetic predisposition to develop a disease, the earlier you learn you're susceptible, the better.

"Together, these efforts can add years to patients' lives and improve their quality of life," says Tavtigian.

CROWDSOURCING SOLUTIONS

Since patientslikeme.com launched in 2006, patients have been sharing their personal data—and information about treatment plans—through cyberspace. Such online platforms produce a unique repository of patient-produced data.

With rare cancers, banding together may be one of the only ways to derive meaningful answers. Take pancreatic cancer. It's the fourth-deadliest cancer in the United States, but only receives 2 percent of the research dollars. Seventy-five percent of patients present with advanced disease and die within a year of diagnosis.

"Pancreatic cancer patients are typically offered only one of three standard of care options, none of which has proven effective over the long term," explains Ocean, who is co-founder of two advocacy nonprofit groups: Let's Win, for pancreatic cancer patients, and Michael's Mission, for colorectal cancer. "Time is of the essence with pancreatic cancer, so our goal with Let's Win is to help patients access science-driven information about treatment options that go beyond 'standard of care' and share that information with their physicians."

The Group Advantage

At HCI, cancer researcher Jakob Jensen, Ph.D., and his colleagues are developing a smartphone app called MoleShare that allows users to post pictures of concerning moles and gain near instantaneous insight about whether they should get it checked out.

"We are just beginning to understand that groups are better than individuals at spotting trouble," says Jensen, whose research has found that people tend to think most moles appear normal. So even if only 19 percent of people are concerned about a mole, you probably should be concerned.

Jensen is on a mission to put together a crowd that spots suspicious moles, then harness the characteristics of the crowd to create a cloud-based virtual crowd that performs just like the human one.

BUILDING A SUPERHIGHWAY

Data silos are starting to break down as some of the biggest names in cancer take steps to actively free data for public use.

Some of these institutions, such as St. Jude, MD Anderson and the Parker Institute for Cancer Immunotherapy are already sharing entire data sets.

Health authorities claim this "freeing of data" for a disease that knows no borders will enable researchers to develop targeted, personalized therapies that improve outcomes for cancer patients. And it will free researchers to make discoveries, too.

"There's a sweet spot we'd all like to get to where physicians who are on the front lines can use data effectively for decision support, but also reuse the same data in a research capacity to better understand the disease and develop more targeted treatments," says Andy Futreal, Ph.D., chair of genomic medicine and co-leader of the Moon Shots Program at MD Anderson.

St. Jude Cloud

Harnessing giant data sets requires tremendous technological infrastructure. Even with modern computers, downloading public data can take months or even years. After spending nearly two years downloading data points from 1,700 patients, St. Jude's Zhang went on a mission to streamline next-generation sequencing data and analysis tools for other researchers.

The St. Jude Cloud, a partnership between St. Jude, Microsoft and DNAnexus, is the world's largest public repository of pediatric cancer genomics data. Users can access half a petabyte of genomic data within minutes. And these data sets and tools aren't only relevant to pediatrics.

"When you go down to the molecular level, it turns out that 45 percent of the driver genes are shared between adult cancer and pediatric cancer," says Zhang. "For example, some pediatric cancers have a mutation in a gene called MAP kinase. When we looked up this mutation in adult cancer, we found that it also is present in colon cancer, melanoma and bladder cancer."

The goal of the cloud is to break down barriers so scientists who don't have formal training in computer science can still interact with the data. Zhang's team designed the St. Jude Cloud to increase accessibility for what she calls "regular scientists."

"We're not there yet, but we are taking a very complex process and deploying it in a smooth fashion so even a noncomputational scientist will be able to use this computational tool," she says.