MUTATIONS, MEDICATIONS, AND PERSISTENCE

By Jennifer Durgin

Matching patients' genetic profiles with effective treatments requires a highly skilled team of scientists and caregivers, a state-of-the-art pathology lab, and a willingness to chart a new course when needed.

Two years ago, VitaMarie "Vivi" Torres was diagnosed with metastatic pancreatic cancer and told she probably had 6-12 months to live. She was shocked. As the primary caregiver for her husband, who has Alzheimer's, Torres was tired but she had no other symptoms.

When her oncologist in Boston outlined her treatment options, she decided to seek a second opinion. She turned to Dartmouth-Hitchcock (D-H), where she met Gabriel Brooks, MD, MPH, an oncologist at Norris Cotton Cancer Center and an assistant professor at the Geisel School of Medicine.

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Greg Tsongalis, PhD, director of the D-H laboratory for Clinical Genomics and Advanced Technology, displays a microchip that can hold millions of fragments of DNA from a single patient.

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BEHIND THE SCENES

While patients with cancer tend to think of their oncologists as the ones directing their care, at a comprehensive cancer center like Norris Cotton Cancer Center, a team of pathologists and scientists collaborate to figure out the very best treatment for each patient. And when patients choose Norris Cotton Cancer Center, they are tapping into one of the most forward-thinking and technologically advanced pathology labs in the country.

The D-H pathology lab was among the first in the country to routinely perform next-generation gene sequencing on patients' tumors, beginning in 2013, to reveal genetic mutations that are driving a tumor's growth. The lab is also one of five designated gene-sequencing centers for the National Cancer Institute's precision medicine treatment trial, dubbed MATCH.

"Gene sequencing used to be very manual and examine only one fragment of DNA," explains Greg Tsongalis, PhD, director of the D-H laboratory for Clinical Genomics and Advanced Technology and a professor at Geisel. "With next-generation sequencing, we can put millions of fragments of DNA from one patient sample on a small chip." The chip, which measures about one inch square, is inserted into a machine that churns out data that is then analyzed by bioinformatics specialists and pathologists.

Cancers have traditionally been defined by their primary location—lung, breast, prostate, pancreas—and how they look under a microscope. But that framework is starting to break down as oncologists and pathologists discover that classifying tumors based on their genetic mutations can sometimes provide critical insight into which treatment to use.

That's why Tsongalis and his team were especially excited when they discovered a rare mutation in VitaMarie Torres's biopsy sample. Not only did she have a rare form of pancreatic cancer, but she also had a rare mutation called an SND1-BRAF fusion, which is very difficult to detect, according to Tsongalis. The discovery was good news because a medication called Mekinist (trametinib) has been shown to extend the lives of patients with SND1-BRAF fusions in other cancers.

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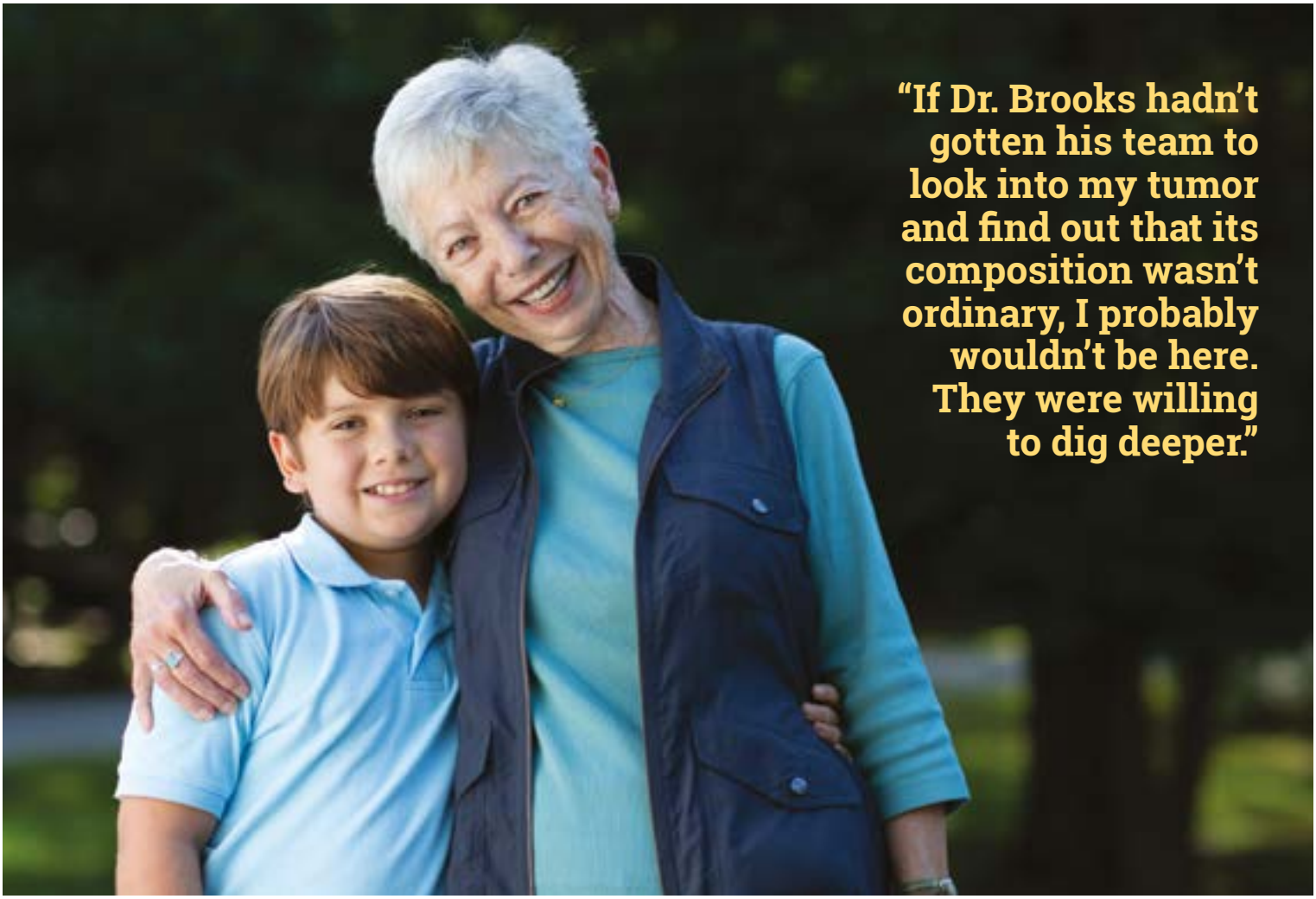


VitaMarie Torres, a patient at Norris Cotton Cancer Center, enjoys many hours a week with her grandson, Asher, including picking him up from school and driving him to soccer practice.

The Hard Science of Precision Medicine

The concept behind precision medicine in cancer is relatively simple: identify a genetic mutation or cellular process that is contributing to the growth of a tumor and block that action. But discovering, developing, testing, and prescribing such targeted therapies is anything but simple.

KONSTANTIN DRAGNEV, MD

Finding the right drug for the right patients

"Cancer is not a single disease," explains Konstantin Dragnev, MD, a professor of medicine and the Irene Heinz Given Professor in Pharmacology at Geisel, who is also a lung cancer specialist at Dartmouth-Hitchcock. "While under the microscope cancer cells may look the same, their genetics may be very different."

In addition, tumors often have more than one dysfunctional cellular process, or pathway, fueling their malignant growth. It follows, then, that an effective way to treat many cancers may be in combining treatments. That's a strategy that Dragnev, associate director for clinical research at Norris Cotton Cancer Center, pursues in the laboratory and in clinical trials. Pharmaceutical companies are often hesitant to invest in combination therapies because of proprietary concerns and the potential for more toxicities. But Dragnev and others have found a way forward.

"We've focused on having very strong preclinical evidence, using an investigational drug in combination with an approved drug, and working with industry partners who welcome this approach," says Dragnev. His pursuit of new cancer therapies is beginning to yield results for patients. Dragnev is helping to lead several clinical trials—one of which grew out of a discovery he and a colleague made more than 15 years ago. "That's how long this work can take," says Dragnev. "It requires persistence and optimism."

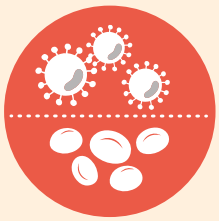
YOLANDA SANCHEZ, PHD

Discovering the cancer drugs of tomorrow

It takes decades of scientific investigation, big data analysis, and preclinical studies before a targeted therapy makes it to a patient's bedside. That process starts with identifying the characteristics of cancer cells that could make them vulnerable to treatment.

"We then screen tens of thousands of chemical compounds to find ones that can target cancer cells' weaknesses and test the most promising compounds in tumors grown from patients' samples," explains Yolanda Sanchez, PhD, associate professor of molecular and systems biology at Geisel and associate director of basic sciences at Norris Cotton Cancer Center.

Sanchez is also working on better ways to identify patients who might benefit from a targeted therapy. She and 12 collaborators from around the country recently published a study about a promising new method to identify malfunctioning cellular pathways in cancer, regardless of the genetic mutation that caused the malfunction. The researchers' innovation is two-fold—focusing on m-RNA (molecules that indicate which genes are turned on) and using machine learning (training computers) to find tumors that are using an errant cellular pathway to grow. This new method can help scientists to identify compounds with the potential to be developed into effective drugs—and may one day allow physicians to better predict which patients will benefit from which targeted therapies.



JOHN X.J. ZHANG, PHD

Building better diagnostics and monitoring

"Biopsies are limited by location and frequency," explains John Zhang, PhD, a professor at Dartmouth's Thayer School of Engineering and member of Norris Cotton Cancer Center. This means that patients' diagnoses and treatment plans are based on samples that are taken in one location in the body—usually the primary tumor site—and at one point in time.

"Cancer is very smart. It's changing all the time in the body," says Zhang, whose lab focuses on building easy-to-use, low-cost, microchip technologies to detect and analyze rare biomarkers—such as circulating cancer cells and the bits of DNA and debris that tumors shed into the bloodstream. Such "liquid biopsies," as they are called, could provide a new and less invasive approach to improve cancer detection, diagnosis, and treatment monitoring. One of Zhang's technologies is being developed for market by NanoLite, a company he cofounded. The NanoLite CellRich system is already in use in Asia and is undergoing clinical trials necessary for approval in the U.S.

Zhang is also collaborating with the director of the Dartmouth-Hitchcock laboratory for Clinical Genomics and Advanced Technology, Greg Tsongalis, PhD, to develop a way to detect pancreatic and prostate cancers early, before they have spread to other locations in the body and become difficult to treat.

Gabriel Brooks, MD, MPH, is an oncologist at Norris Cotton Cancer Center and an assistant professor of medicine and of The Dartmouth Institute for Health Policy and Clinical Practice.

"If this therapy can help her live a fulfilling life today and tomorrow and over the coming months, that's the point of it."

Targeted therapies rarely cure a patient's cancer, but such medications can extend life by months or years, even for advanced cancers.

Brooks took this information to the Cancer Center's Molecular Tumor Board—a group of oncologists, pathologists, scientists, and other specialists who meet regularly to review the test results of individual patients, scour the scientific literature, and tap into their collective knowledge to recommend the most promising treatment options. Together, they agreed that trametinib was, theoretically, the best option. The problem was that they could find no reports of the targeted therapy being used for pancreatic acinar cell carcinoma, and that use was not approved by the U.S. Food and Drug Administration.

UNCHARTED WATERS

"So even though we had a rationale—it looked like the drug should work—there was no published data for this plan," explains Brooks. The tumor board had recommended that Torres apply to a clinical trial that would have given her access to the drug, but her application was denied. She didn't meet the enrollment criteria. And at a cost of $12,000–$13,000 per month, Torres could not afford the medication on her own.

Brooks and Torres faced a difficult decision: continue to push for the theoretical treatment or enroll in a clinical trial with a different class of medications that she was eligible for and could potentially benefit from.

"As an oncologist, it's hard to give someone a treatment for which there's no human data for their particular cancer," explains Brooks. "How could I recommend trametinib as a first-line or even a second-line treatment when we had a different clinical trial that might help her?"

Precision medicine—matching treatment plans with patients' unique genetic profile—is still not an exact science, in part because the science is evolving so rapidly. Likewise, targeted therapies rarely cure a patient's cancer, but such medications can extend life by months or years, even for advanced cancers.

Brooks and Torres decided to enroll her in a clinical trial that they hoped would stop her cancer from progressing. But after several months, it was clear that the treatment was not working.

It was the fall of 2017, and Torres was nearly out of options. Brooks suggested they make one more push to try to get her access to trametinib. When Torres's health insurance company denied coverage of the treatment, the next step was to petition Novartis, the drug's manufacturer.

Brooks enlisted the help of Lanelle Jalowiec, an oncology resource specialist at the Cancer Center, who helps patients to apply for grants to cover their medication co-pays and to access free medications from pharmaceutical companies. Even with good insurance, notes Jalowiec, patients typically face out-of-pocket costs of $3,000 per month for oral cancer medications.

"My goal is to get patients the right medication at the lowest cost as quickly as possible and to minimize patients' stress," says Jalowiec. Within a couple weeks, Jalowiec succeeded. Novartis agreed to provide one year of trametinib to Torres at no cost. She took her first dose in November 2017.

PERSISTENCE AND PROMISE

Getting access to trametinib was good news for Torres, but even better news came at her first follow-up appointment after starting the medication. A blood test revealed a dramatic decrease in CA19-9—a biomarker indicating tumor activity that had been steadily climbing since her diagnosis. More good news followed in March 2018, when a CT scan showed no new growth in the primary tumor nor metastases.

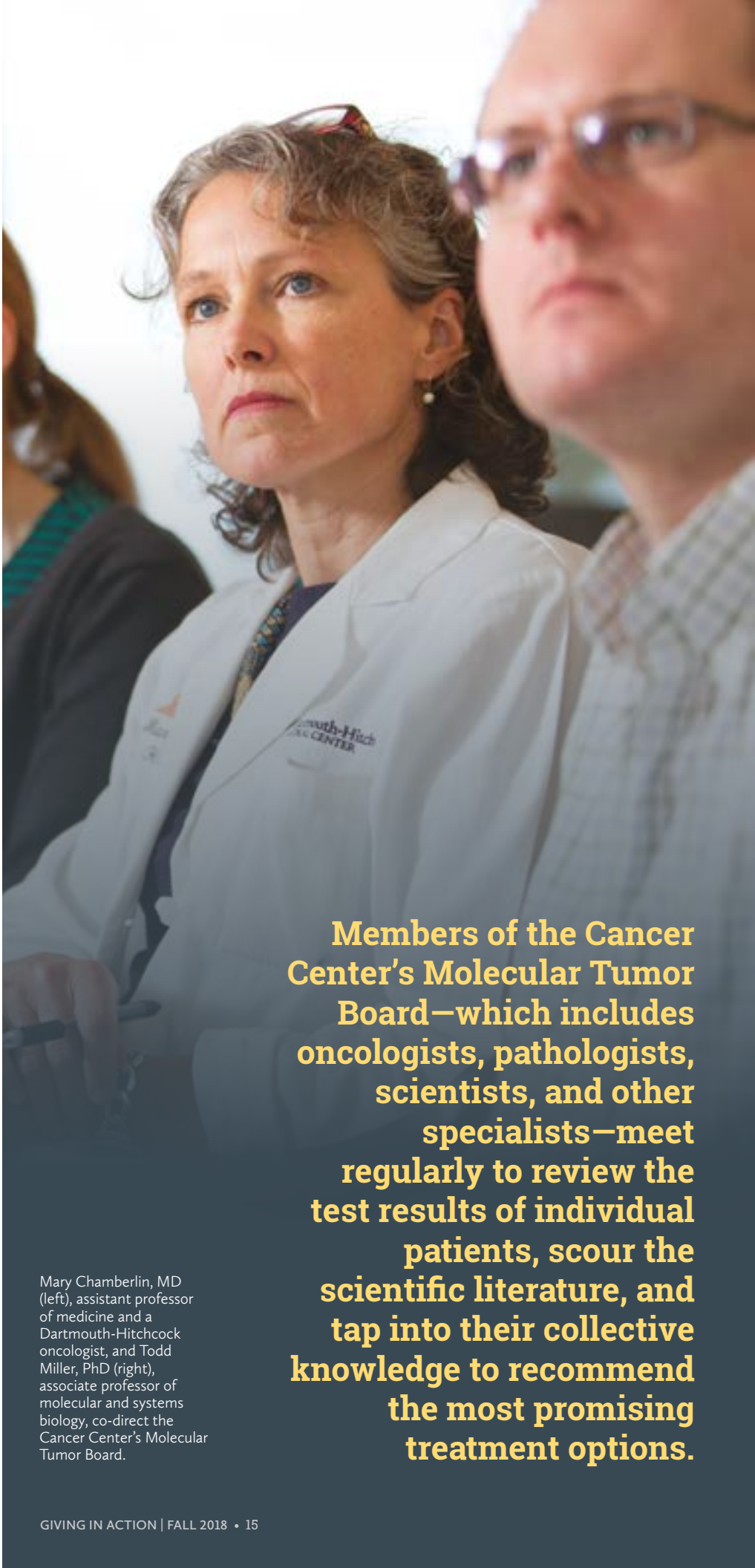
"The truth is this may stop working at any time," cautioned Brooks. "But if it can help her live a fulfilling life today and tomorrow and over the coming months, that's the point of it."

Brooks's warning came true in September, when imaging tests showed that tumors on Torres's pancreas and liver had grown; her cancer had become resistant to the targeted therapy.

Though Torres faces new uncertainty and treatment decisions, she is grateful for the many months she has enjoyed with a relatively good quality of life. She has been living her life to the fullest, spending several afternoons a week with her nine-year-old grandson, attending his soccer games, playing bridge, walking regularly, and even traveling to California earlier this year. "The fact that she is alive with a good quality of life is remarkable," says Brooks.

Although the gains for patients like Torres may seem incremental, the future of precision medicine is bright. As the science advances, many more patients will be outliving their prognoses and living life to the fullest. Less toxic treatments, longer lives, and, eventually, cures—those are the promises of precision medicine in cancer.

"If Dr. Brooks hadn't gotten his team to look into my tumor and find out that its composition wasn't ordinary, I probably wouldn't be here," says Torres. "They were willing to dig deeper." And that persistence has made all the difference in the world to Torres and her family.



Members of the Cancer Center's Molecular Tumor Board—which includes oncologists, pathologists, scientists, and other specialists—meet regularly to review the test results of individual patients, scour the scientific literature, and tap into their collective knowledge to recommend the most promising treatment options.

Mary Chamberlin, MD (left), assistant professor of medicine and a Dartmouth-Hitchcock oncologist, and Todd Miller, PhD (right), associate professor of molecular and systems biology, co-direct the Cancer Center's Molecular Tumor Board.