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Both of these women have brain tumors.

One is beating the odds.

CLOSING THE CANCER GAP

BY ALICE PARK

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Marcia Stiefel, 68
North Dakota

Stiefel spent Thanksgiving in the hospital to have a brain tumor removed; now she awaits the results of scans that will tell her whether the radiation and chemo worked

HEALTH

The Cancer Gap

No two cancers are alike. But what will it take to give every patient equal care?

By Alice Park

Photographs by Christopher Morris for TIME

LAST YEAR, A WEEK BEFORE Thanksgiving, Marcia Stiefel was backing out of her driveway in Bismarck, N.D., when her left side went weak. "I noticed I didn't have peripheral vision," she says. And after she overshot the drive and hit a fence, twice, she asked her son to drive her to the hospital.

She thought she'd had a stroke, but an MRI revealed something else: a brain tumor called glioblastoma the size of a golf ball. Her doctors wanted to move quickly—her cancer was already Stage IV—so instead of celebrating the holiday cooking for the 10 people she was expecting, including her two sons and their families, Stiefel spent it at the hospital recovering from surgery and preparing for the dual onslaughts of radiation and chemotherapy.

On the list of cancers with the worst prognoses, glioblastoma is near the top. Doctors tend to rank cancers by the likelihood a patient will be alive five years after treatment. That's the magic mark beyond which people have a better chance of beating a disease altogether. With glioblastoma, within a year or two of diagnosis, 75% of patients are dead.

By some cruel coincidence, Stiefel, 68, knew this already. Her husband died of the same cancer in 2009, after a seizure. His surgery to remove the tumor left him unable to speak or go to the bathroom without her help. "My first thought was that I was going to go like him," says Stiefel, who lives in an assisted-living facility but manages well without around-the-clock care. "I would cry all the time. I didn't want to know that I was dying."

Neither did MaryAnn Anselmo, 59, who spent her Thanksgiving much the same way just a year earlier. A jazz singer who lives with her husband in New Jersey, she learned she had advanced glioblastoma after a dizzy spell sent her to her doctor. She'd already endured six weeks in intensive care after a car accident a year and a half earlier, and the latest diagnosis felt like the final blow. "I thought, Somebody wants me dead here for some reason."

Both women's doctors opted first for the blunt-force approach that's standard for most cancers: surgery, radiation, chemo. But glioblastomas have an insidious habit of infiltrating brain tissue with tiny fingers of malignant cells, making the tumors hard to treat the traditional way. That's why, even after treatment, they almost inevitably come back.

There's a better way of attacking glioblastoma, or at least doctors think there is. It's still at the experimental stage, but when Anselmo's body couldn't tolerate the chemo, she eventually became among the first patients to take the risk and test it.

First, Anselmo's doctors at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City sequenced her tumor's DNA. If it contained any of the few hundred mutations they know can prompt healthy cells to grow uncontrollably—that's what cancer does, after all—her doctors could then check her mutations against databases of ongoing clinical trials to see whether she'd be eligible for experimental drugs that might do some good.

The decision to test wasn't a difficult one for the team at MSKCC; the hospital always has a lot of clinical trials under way, and once they sequenced her tumor, they had reason to believe Anselmo might be a good candidate for a drug being tested in one of them.

Though it's still early days, the technology and the promise it holds are irresistibly exquisite. But it isn't available everywhere, and that's where Anselmo's care diverges from Stiefel's. At Sanford Health in Bismarck, if oncology director Dr. Thandiwe Gray profiles a tumor and finds a mutation, there's very little chance she will be able to refer her patient to a trial, regardless of how promising the medication seems. Her hospital simply isn't running as many clinical trials, which require a steady flow of patients with a variety of different cancers to fill the testing slots. And what if the testing spits out mutations for which doctors don't have any drugs, even unproven ones they want to try? What then?

For now, these two women with the same diagnosis are case studies of where cancer care is today and what it will take to bring it to a point, in the not-too-distant future, where doctors say it needs to be.

The Promise of Precision

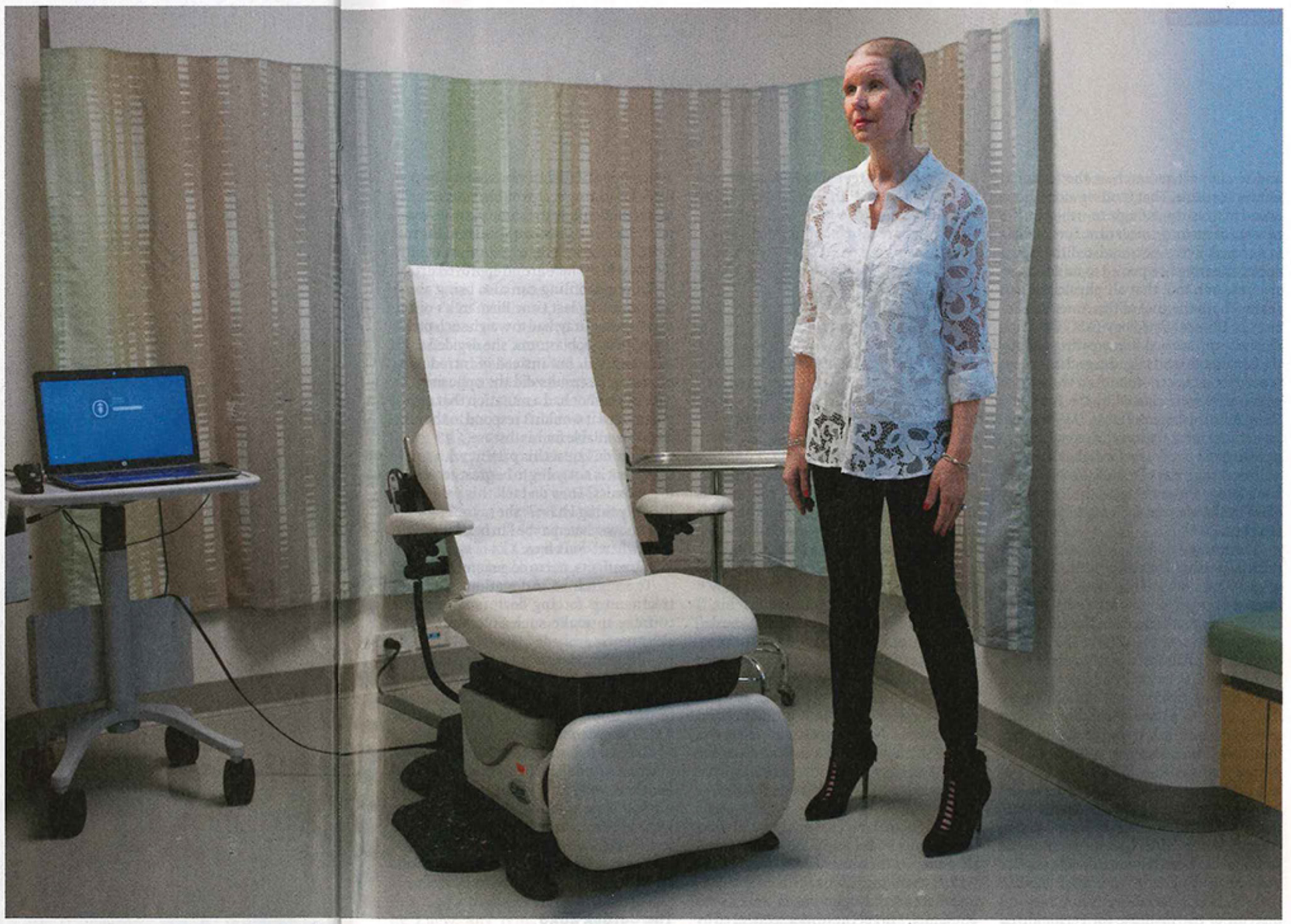
THE WAY CANCER HAS BEEN TREATED FOR the past several decades has been the standard of care for a reason: it's been studied—a lot. But the calculus that favors the tried and true over the intriguing but experimental is being undermined by a radical reconception of what cancer is and what propels the malignancies that resist treatment and take so many lives.

No two cancers are alike; even within an individual patient, tumors may change over time. And doctors are learning that a melanoma growth might have more in common with a lung cancer or a brain cancer than another melanoma. "We are moving away from the concept that all lung cancers are the same and all breast cancers are the same and all colon cancers are the same," says Dr. David Solit, director of the Kravis Center for Molecular Oncology at MSKCC. "Now we are going to know if you have EGFR mutant lung cancer or an ALK fusion lung cancer or a BRAF mutant brain cancer. And we are going to know better ways to treat those cancers based on those mutations."

That's led to a new consensus that to truly fight cancer, doctors need to understand it from the inside out, which means decoding its DNA and exposing the ways it co-opts the body's healthy cells. Once that's known, the task becomes to develop drugs that can thwart the way a given cancer wrecks the body. Until recently, this highly sophisticated approach to cancer was virtually nonexistent. But fast-moving developments in genetics and molecular biology are quickly changing that. "This type of testing isn't standard of care yet, but everyone agrees it will be at some point," says Solit.

This has come to be known as the precision revolution in medicine, the push to move away from crowd-based, best-for-most treatments like the kind Stiefel is getting, and toward therapies designed to treat an individual patient's ills, as with Anselmo's care. The mantra for the precision approach is to learn from every single patient.

In January 2015, the federal government launched a $215 million Precision Medicine Initiative to help build a database of health information about 1 million Americans



MaryAnn Anselmo, 59
New Jersey

Anselmo's brain cancer is being treated with an experimental drug at Memorial Sloan Kettering Cancer Center in New York City; her tumor hasn't grown in a year

PREVIOUS PAGES: VII: THESE PAGES: CHRISTOPHER MORRIS—VII FOR TIME

and to support research at the National Cancer Institute. That funding alone, however, isn't nearly enough to usher in the new era of custom cancer care. For this idea to succeed, every personalized therapy a doctor tries must be pooled to build a massive research tool that all physicians can share. That's the goal of the American Society of Clinical Oncology (ASCO), which recently announced it is creating a registry of patients who take drugs that are approved for a cancer other than the one for which they were cleared by the Food and Drug Administration (FDA). "We want to gather that information and see what happens to those patients, even if they aren't in a clinical trial," says Dr. Julie Vose, chief of hematology and oncology at the University of Nebraska Medical Center and president-elect of ASCO.

She knows that such treatments, as with anything bespoke, will take lots of good data, as well as time, labor and money—which for now aren't distributed equally among hospitals in the U.S.

Currently, less than 5% of the 1.6 million people diagnosed with cancer each year in the U.S. can take advantage of genetic testing, which can run anywhere from $3,000 to $8,000, depending on how many genes are analyzed. At most hospitals, this kind of testing is limited. And even at centers like MSKCC, about 70% of patients' genetic testing is not covered by insurance, so the program operates at a loss. For its part, the University of Texas MD Anderson Cancer Center in Houston funds its testing almost entirely with donations. "It's clearly not a long-term sustainable model," says Dr. Funda Meric-Bernstam, medical director of the Institute for Personalized Cancer Therapy there.

There's also the reality that too much information—and a dearth of sophisticated drugs—could lead to gambles. Doctors now know of a few hundred mutations linked to cancer, but there are targeted therapies for only about 20 to 40 of them. "If an early-stage cancer is curable with standard care, identifying a mutation just adds anxiety to the patient and might provoke the doctor to do something stupid," says Meric-Bernstam.

Who will guide doctors to make smart decisions? How will they decide when to test and when not to test? Regulatory agencies like the FDA, which greenlights drugs for human use, will also have to play serious catch-up and review the drug-approval process. "Doctors and patients are way ahead of where the FDA and insurance companies are in using different medications," says Vose. And with lives in the balance, those doctors aren't likely to slow down anytime soon.

Not Yet an Even Playing Field

"FOREVER AND EVER IS WHAT THEY TELL me," says Stiefel about how long she has to take the four chemo pills she swallows five days a week each month. She started her chemo regimen at the same time her six weeks of radiation began.

The combination is a brutal one-two punch, and it's supposed to be—to knock out as many of the lingering cancer cells as possible. It robbed Stiefel of her hair and sapped her energy; she still sleeps a lot, and for a while, the only thing that would wake her was the bouts of nausea that would hit at all hours.

Her usual optimism also took a hit. "I didn't want to be out of control, but you definitely are out of control because the prognosis is just so devastating," she says. For help, she turned to a therapist, who taught her positive-thinking techniques and prescribed antianxiety and antidepressant medications. Now beginning her second round of chemo with a higher dose, she says, "You have to put some faith in what the doctors say. You only hope they know what's best for you."

Her doctors meet weekly to discuss every cancer case at the hospital. When they suspect the presence of mutations for which there are FDA-approved drugs—and there are only a few dozen—they send out samples to get the tumor sequenced by an outside institution. But if there are no drugs available, which is more often the situation, says Dr. Tarek Dufan, medical director at the Bismarck Cancer Center, the decision is not to test.

Less than 5% of the 1.6 million Americans diagnosed with cancer each year can take advantage of genetic testing

Even if Stiefel's tumor were to be profiled, for example, it wouldn't necessarily mean she'd follow the same path as Anselmo's. Stiefel's tumor could fall into the majority of mutations that doctors can identify but for which there are no approved drugs.

Tumor profiling can also bring about impasses. The last time Bismarck's oncology director, Gray, had to weigh such profiling with a glioblastoma, she decided to go ahead with it. But instead of introducing promise, the results did the opposite. The patient's tumor had a mutation that nearly guaranteed it wouldn't respond to the only chemo available for his disease.

"How do I treat this patient with something that is not going to be great according to genomics? How do I tell this patient it's the only thing I have?" she says. "I figured, You know what, maybe I'm better off right now, when I don't have a lot of agents to offer my patients, not to do genomic testing."

The march of innovation in cancer treatment is forcing doctors around the country to make such Solomonic decisions nearly every day. "Right now, genetic profiling is giving us interesting information on some patients, but we are at a point where we don't know what to totally make of that information yet," says Vose, the ASCO president-elect.

Gray ended up giving that patient the chemo, and defying the odds, he lived another two years. If the genomic testing had been absolutely correct, he likely wouldn't have survived so long. So was the test wrong? Did the chemo work? Did the patient just get lucky? Those are questions Gray—and science—can't yet answer.

The Cutting Edge

WHEN ANSELMO WAS REFERRED TO DR. David Hyman, acting director of developmental therapeutics at MSKCC, it was because she was out of options. Her surgeon had removed 75% of her tumor, but the rest was too enmeshed in her brain to scrape away safely. On Christmas Day, she took her first chemo pill, and the next day she began six weeks of radiation.

But within weeks, her immune system started to crash, and after she'd been on the drug about a month, her doctors took her off it. Her only other option, Avastin, is the second-line therapy for a reason; most tumors start growing again after just four months.

Because glioblastoma is so hard to treat, Hyman had already ordered a genetic test of her tumor after surgery. And on the basis of the results, he thought she should join a trial he was running.

His study, which is called a basket trial, pulls together people with 20 different types of cancers—including brain tumors like Anselmo's, lung cancers and colon cancers—whose tumors all share the same genetic mutation. MSKCC's genetic test scans for known aberrations in 410 genes that have been linked to cancer. In Anselmo's case, her doctors learned that her brain cancer is driven by a mutation called BRAF. While common in melanoma, the mutation is rarer in glioblastoma. Basket trials are an efficient way of seeing whether different cancers with the same mutation respond in the same way to a drug that's designed to hijack it. And that's what MSKCC is testing on Anselmo and others with a drug called vemurafenib, which was approved in 2011 for melanoma.

Of course, there are no guarantees. Even if they share the same mutation, cancers that start in the skin, where cells divide and die more rapidly than almost anywhere else in the body, are almost certainly a little different from cells in the brain, which are more protected and conserved. The side effects of such drugs are largely unknown. It's also a complete mystery how many of the people in the basket will be alive a year, two years, and five years after taking the drug.

When Hyman first met Anselmo he really wanted to offer her something. Weak from the radiation and what little chemotherapy she could tolerate, she was in a "bad situation." Without the chemo, he knew, any remaining cancer cells would inevitably start to grow again, some venturing beyond the brain to other parts of her body.

"It's an awful disease to watch a patient suffer from," Hyman says. "They become weak, and that changes their personality. It saps them of what makes them them."

Hyman knew how effective vemurafenib is on BRAF melanomas, so he had good reason to hope for—and expect—similar results with Anselmo's brain tumor.

He turned out to be right. She has been swallowing the drug daily for almost a year—longer than her doctors thought she would survive, with or without chemo. Other than a brief rash from treatment, Anselmo hasn't experienced any side effects.

CHRISTOPHER MORRIS—VII FOR TIME

State-of-the-art scanning

This slide contains 96 samples of tumor DNA from MSKCC's gene sequencer, which can decode patients' cancers in 72 hours

(Like Stiefel, she lost most of her hair during radiation, which tends to burn the scalp.) "Every time I go back to have a new MRI taken, they find no growth," she says. So far, the tumor has shrunk an additional 55%.

"It's almost unprecedented to have this type of regression with the currently approved therapy," says Hyman.

As promising as her results are so far, Anselmo didn't know what would happen when she signed up for the trial. Still, choosing to try an experimental drug she was eligible for hardly felt like a choice. But it was still more of a choice than many people with glioblastomas get to make.

Trial and Error

FOR NOW, MANY FACTORS THAT HAVE nothing to do with science determine which trial drugs a patient has access to. There's geography, since most Americans are treated at the hospital closest to home, and most hospitals don't have a lot of clinical trials under way at any given time. There's also money: both a patient's financial situation and that of their cancer center can influence what's available to them.

Finally, there's human temperament—the squeaky-wheel factor, which can at times put patients at odds with science. Doctors know that vemurafenib works on tumors with BRAF mutations, for instance, but simply hearing about the trial at MSKCC may be enough to prompt patients who have not had genetic testing to beg, plead and bargain for access to the drug—and for doctors who might not have anything else to offer them to prescribe it.

Stiefel's doctors anticipate it may come to that, though Gray says she would profile the tumor first. "But I don't want to waste too much time in waiting to test," she says. Stiefel still hasn't had her first scan to see how her tumor has responded to the radiation and chemo.

Unlike Anselmo's immune system, Stiefel's held up to the regimen. But if her glioblastoma proves true to form, it will eventually evade the chemo that Stiefel's doctors say she'll have to take for the rest of her life. But if there are any signs that her cancer is growing again or that it has spread, Gray will try to find out which mutations Stiefel's tumor has. If it contains the BRAF mutation, Gray plans to prescribe the drug even though it's still not approved for glioblastoma. "I will do what I think is best for my patient," she says.

That's possible because doctors have a lot of leeway in the way they prescribe drugs. Any drug approved by the FDA can be prescribed for any purpose, as long as the doctor has reason to. Covering the cost of the drug is another matter. Insurers use FDA approval as a criterion for deciding which drugs to reimburse. So when it comes to off-label prescribing, there's no guarantee that insurance will cover the cost, which in the case of vemurafenib is exorbitant—up to $65,000 for the recommended six-month treatment period. If Gray and Stiefel move forward with that plan, it becomes a matter of "a lot of begging of the insurance company," Gray says, to pay for the drug.

Her efforts, as well as Hyman's and those of thousands of other cancer doctors across the country, share the same goal: to give their patients more than what they have today—to offer them tailored and scientifically tested therapies that have a strong chance of conquering their disease.

There's a reason we fear tumors that arise seemingly out of nowhere and there's a reason we catch our breath when we hear the diagnosis. By its nature, cancer is unpredictable and untamable. But calming the rampant growth one patient and one mutation at a time may provide the best chance yet of finally getting cancer under control.

That's what Stiefel is counting on. "People have told me miracles happen, that they know someone who had this and lived for an extra 15 years," she says. "I just have to stay positive. That's your only salvation." ■