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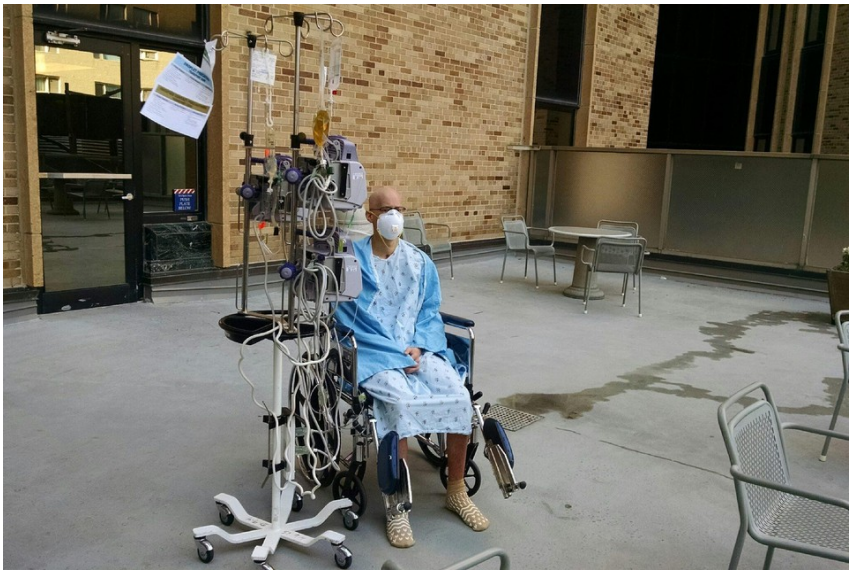
Cancer Treatment's New Direction

Genetic testing helps oncologists target tumors and tailor treatments



Evan Johnson sits on a terrace at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minn. during the summer of 2014. He suffered from an aggressive form of acute myeloid leukemia. *PHOTO: KEN JOHNSON*

By **RON WINSLOW**

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Evan Johnson had battled a cold for weeks, endured occasional nosebleeds and felt so fatigued he struggled to finish his workouts at the gym. But it was the unexplained bruises and chest pain that ultimately sent the then 23-year-old senior at the University of North Dakota to the Mayo Clinic. There a genetic test revealed a particularly aggressive form of acute myeloid leukemia.

That was two years ago. The harrowing roller-coaster that followed for Mr. Johnson and his family highlights new directions oncologists are taking with genetic testing to find

and attack cancer. Tumors can evolve to resist treatments, and doctors are beginning to turn such setbacks into possible advantages by identifying new targets to attack as the tumors change.

Mr.

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Johnson's medical team scrambled to find effective treatments against the genetic mutations driving his disease. His course involved a failed stem cell transplant, a half-dozen different drug regimens, four relapses and life-threatening side effects related to his treatment.

"We truly felt like we were in a war," his mother, Carol Johnson, recalls. "We didn't know where that enemy was at any given moment and what means he was going to use to attack us next."

Evan sits with his older brother, Dain, who was the first stem cell donor, alongside the Mayo Brothers statues in Rochester, Minn. in the summer of 2014. *PHOTO: CAROL JOHNSON*

Nine months in, his leukemia had evolved to develop a surprising new mutation. The change meant the cancer escaped one treatment, but the new anomaly provided doctors with a fresh target, one susceptible to drugs approved for other cancers. Doctors

adjusted Mr. Johnson's treatment accordingly, knocked out the disease and paved the way for a second, more successful stem cell transplant. He has now been free of leukemia for a year.

"You could see the cancer evolution happen," through regular genetic testing, enabling his treatment to be "personalized in real time," says Pashtoon Kasi, an oncology fellow at the Rochester, Minn.-based Mayo Clinic and a member of the team that cared for Mr. Johnson. "This is where oncology is headed down the line."

Just a decade ago, "we were shooting in the dark," says Jose Baselga, physician-in-chief at Memorial Sloan Kettering Cancer Center in New York. If first- or second-line treatments failed, "we either had nothing to do [next], or what we did was totally disconnected with the biology of the disease."

Now patients with advanced cancer who are treated at major centers can expect to have their tumors sequenced, in hopes of finding a match in a growing medicine chest of drugs that precisely target mutations that drive cancer's growth. When they work, such matches can have a dramatic effect on tumors. But these "precision medicines" aren't cures. They are often foiled when tumors evolve, pushing doctors to take the next step to identify new mutations in hopes of attacking them with an effective treatment.

The Johnson family from left to right, Connor, Dain, Carol, Ken, Evan and Ross in Rochester, Minn. at Christmas 2014. *PHOTO: EMBE PHOTOGRAPHY*

"It's like a Whac-A-Mole game," Dr. Baselga says. As soon as a new mutation surfaces, the strategy is to find a new hammer to hit it with.

The approach is challenging. There aren't drugs to treat many cancer-causing

mutations. When drugs exist, there is no guarantee they will work. A drug that works for a melanoma patient may not succeed in a colon-cancer patient with the same mutation, for example.

Moreover, DNA tests of tumors may lead to a recommendation for a drug that isn't approved for the type of cancer being treated, jeopardizing reimbursement for drugs that typically cost $10,000 or more a month.

"It's not for every patient or cancer," Dr. Kasi says. "But as we develop more drugs and understand more [treatment] pathways, it would be a reasonable option for a lot of our patients."

EVAN JOHNSON'S PATH TO REMISSION

- **February 2014:** Diagnosed in Grand Forks, N.D. with acute myeloid leukemia and flown to Mayo Clinic in Rochester, Minn. A genetic test revealed a certain mutation in the FLT3 gene that is a marker of a poor prognosis.
- **April:** Started on sorafenib, a drug that targets FLT3, plus a cancer drug called 5-AZA.
- **May:** Received a stem cell transplant considered a perfect match. He relapsed after 67 days.
- **August to December:** Evan participated in a trial of an experimental AML drug and doctors tried a series of drugs, including a clinical trial. Evan had a sustained response for four months.
- **November:** A test showed initial evidence that Evan's cancer was developing a new genetic alteration known as the Philadelphia chromosome, a finding that surprised his doctors. Evan relapsed in January.
- **January 2015 to March 2015:** Doctors tried several drugs including ponatinib, which attacks both FLT3 and the Philadelphia chromosome—further tailoring treatment to the molecular traits of his cancer.
- **April:** After achieving a remission with no evidence of leukemia cells, Evan underwent a second stem cell transplant from an unknown matched donor. The procedure worked.
- **March 2016:** Nearly one year out from the second transplant and two years after his initial diagnosis, he is in remission.

Dr. Kasi and his Mayo colleagues—Naseema Gangat, a hematologist, and Shahrukh Hashmi, a transplant specialist—are among the authors of an account of Mr. Johnson's case published in January in the journal Leukemia Research Reports.

Mr. Johnson's first genetic test at Mayo, in February 2014, revealed that his cancer was driven by a mutation in a gene, called FLT3, that is usually associated with a poor prognosis. His best chance at survival was a stem cell transplant. More than 50% of the blood cells in his bone marrow were myeloblasts, or blasts for short, dysfunctional immature cells that are a hallmark of the disease. Before qualifying for a transplant, a patient's blasts need to be under 5%.

To get under 5%, he started on a standard chemotherapy regimen and almost immediately, things went south. His blast cells plummeted, but "the chemo just wiped out my immune system," Mr. Johnson says, likely opening the doors to a mysterious fungal infection that attacked his throat and nearby soft tissue. Emergency surgery failed to help.

Just 10 days after his arrival at Mayo, a surgeon tearfully told the family that Mr. Johnson had a 10% chance of surviving the next 48 hours, Ms. Johnson says.

Evan Johnson in Maui in March 2013. *PHOTO: WESIDE PHOTOGRAPHY*

The next day Mr. Johnson's three brothers bought an expensive golf driver he'd been eyeing and placed it in his hands as he lay tethered to tubes in the ICU. They sensed he responded with a faint smile.

Then as mysteriously as it began, the infection stopped. But Mr. Johnson couldn't tolerate the chemo, and his blast cells were on the rise. A two-drug combination that included the liver cancer drug Nexavar, which targets the FLT3 mutation, knocked back the blast cells. But the stem cell transplant in May, which came from one of his brothers, failed to take, and he relapsed after 67 days, around late July.

By then, his ordeal had taken a toll: the throat surgery left him unable to swallow and he weighed just 120 pounds, some 55 pounds less than the day he arrived.

He was put into a clinical trial of an experimental AML drug being developed by Astellas Pharma of Japan. To participate, Mr. Johnson had to be able to swallow a pill. It took weeks of exercises with a swallowing coach and bags of M&Ms, but he succeeded just before the trial opened at the clinic in September.

The trial was almost a respite for Mr. Johnson. Free of toxic chemotherapy, his hair came back. He started to regain weight, an important consideration, as his doctors wanted him healthy enough to eventually try a second transplant. His blast cells were responding well to the medicine.

The Johnson family at Thanksgiving of 2015 at the Gift of Life Transplant House in Rochester, Minn. From left to right, Ross, Carol, Evan, grandmother Anita Harrang, grandfather Philip Harrang, aunt Louise Shapiro, Connor, cousin Nathan Shapiro, Dain. *PHOTO: DENNIS LAMERS*

In November 2014, doctors spotted the initial signs in blood tests that Mr. Johnson's cancer was evolving to acquire a new mutation. By late January, he relapsed again.

To the doctors' surprise, the culprit was the Philadelphia chromosome, a well-known genetic alteration associated with chronic myeloid leukemia. It also is a target of the blockbuster cancer drug Gleevec and several other medicines.

Armed with new options, the Mayo team revamped Mr. Johnson's treatment, starting with a regimen that included chemotherapy and Sprycel, a next-generation version of Gleevec.

His fight wasn't over. He developed lung inflammation and other side effects on the new medicine and relapsed yet again. Taking a suggestion from a national expert panel on AML, doctors switched to a regimen including Iclusig, a drug that hits both FLT3 and the Philadelphia chromosome.

The total cost of Mr. Johnson's care was $4 million, says Ms. Johnson, adding that the copayments for his treatment were manageable. None of the key drugs given to Mr. Johnson are approved for AML, meaning most were used off-label. That is a deal breaker for many insurers, who balk at paying for expensive drugs for nonapproved uses. But Dr. Kasi says the Johnsons' health insurer was "responsive" to Mr. Johnson's needs.

Tests using the most sensitive instruments showed Mr. Johnson had no blast cells, which Mayo's transplant experts set as a prerequisite before performing another transplant. This time the donor was an anonymous person from Germany, under a

program called Be the Match that keeps a global registry of willing stem cell donors. He got his second transplant last April. After he recovered from several weeks of severe side effects including pancreatitis, recent tests suggest he has a good chance of a sustained, durable remission.

Mr. Johnson finally returned home last summer after 17 months at the Mayo Clinic. He is now finishing his senior year in college. He says he was too weak last year to give his new driver a good test on the golf course. He expects a better chance this summer.

Write to Ron Winslow at ron.winslow@wsj.com