

To Make Progress in Rare Cancers, Patients Must Lead the Way

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In January, 2004, I flew to New Orleans, LA, to meet Andy Martin. He took me to the laboratory where he was working. A third-year medical student, he was trying to get tumor cells to grow to run experiments on them. The tumor cells were his own.

Only 31 years old, Andy had been diagnosed with sinonasal undifferentiated carcinoma, or SNUC—a rare, lethal cancer. Even after an exhaustive search of the medical literature, he found fewer than 100 documented patients. Recognizing that a cancer so rare was unlikely to be studied by anyone else, Andy donated tissue from his own tumor and launched a study. Eleven months after our meeting, he died.

In that short time, he pushed forward the study of SNUC. After extensive research and experimentation, he succeeded in getting the cells to grow, one of the first steps in the long process to research and find effective therapies for a disease.

Lately, I have been thinking about Andy. During the past year, I identified and studied a range of potential new models for advancing the study of rare cancers, those with fewer than 40,000 diagnoses a year. There are more than 200 such cancers, and they represent an estimated 25% of cancer mortalities, yet for the most part they are underfunded and understudied. Many remain intractable, with treatments and mortality rates that have not budged in decades.

For years, the typical approach has been that most of our resources and attention must focus on more common cancers, which still kill so many people every year. The assumption was that any advances made in these tumors would eventually benefit all people with cancer. But what we now know is that there are subtypes of tumors even among common cancers. It is urgent that as many pathways and targets as possible be studied and that we launch an initiative focusing resources and attention on rare cancers. The experience of Andy and other patients that I interviewed offers a way to do it.

Andy ended up working with physicians who were his partners in an effort to find more effective therapies. Andy had time to research SNUC in a way that none of the physicians did. They were not SNUC specialists and had many other patients to

treat. They recognized that when it came to SNUC, Andy was in many ways the expert on the disease. These physicians learned from the research he did, and used it to help guide him in the choices he made.

When Andy wanted to study his own tumor in the hopes of driving research into the disease, he sought out Tyler Curiel, MD, who was then the head of the hematology/oncology department at the medical school where Andy studied. Andy's idea was to work in Curiel's laboratory. On that visit to New Orleans, Curiel told me that at first, he turned Andy's request down. Curiel knew that Andy did not have extensive laboratory experience and would need support for his work. Curiel feared that running a project might offer him false hope about what he could realistically achieve given the prognosis of his disease. He was also concerned that removing part of Andy's tumor to study it might harm him.

But even amid all these reservations, Curiel says he realized something: medicine at that moment did not have a cure or even an effective treatment to offer Andy. "If I can't cure his cancer," Curiel told me he reasoned to himself when debating Andy's proposal, then "why not let him take charge of it?"

Once Curiel made this decision, he found a way to address his other concerns. One of the researchers in the laboratory volunteered to work with Andy in his spare time to supervise his work. The surgeons came up with a less invasive way to remove enough tumor to launch the study without harming Andy. When Andy's efforts started to look promising and they realized they needed more money to keep the project going, Curiel and the university community held a fundraiser that brought in \$28,000, a pittance in the world of drug development, but enough to allow Andy to figure out how to get the cells growing, something that had never been accomplished before. Andy always knew that the odds they would find a drug in time to save his life were low, but that small sliver of hope gave his life meaning and purpose and fueled a scientific search that he believed might ultimately help save others.

The search continued even after Andy's death. At the entrance of Curiel's current laboratory at the University of Texas Health Science Center at San Antonio hangs a picture of Andy, a reminder to the

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researchers of why they need to work quickly. Curiel is now collaborating with a group headed by Ehab Hanna, MD, at M. D. Anderson Cancer Center, Houston, TX, on a project to use molecular profiling tools to study tumor samples from recently treated SNUC patients in the hopes of finding potential new drug targets. They are also studying the medical records of the 60 to 70 SNUC patients treated at M. D. Anderson over the years to try to glean more information on the course of the disease and how patients responded to therapy. Once this study is published, it will represent the largest data set of SNUC patients to date. It was Alexander Gelbard, a head and neck surgical resident at M. D. Anderson and Andy's medical school roommate, who pushed the current project. He says he was inspired working alongside Andy in Curiel's laboratory. "I learned that in these kinds of rare cancers, patients play a big role in getting things to start moving," he told me.

Patients with rare cancers have long tried to draw attention to their plight. They have lobbied the National Institutes of Health, Congress, and other institutions to fund research into particular diseases. They have raised money to support projects and founded groups that provide critical patient support and educational materials. These are all valuable contributions. But more needs to be done, and these efforts underscore a key point: rare cancers will never be a priority unless the patients make it one. As Andy and others argued, patients themselves must therefore play a larger role in driving forward the search for therapies.

Jeffrey Kaufman realized this after his wife, Marnie, was diagnosed in 2004 with adenoid cystic carcinoma (ACC), a rare salivary gland cancer. Surgery and radiation can treat the cancer. But most patients eventually experience recurrence of the disease, and when they do, there are no effective therapies.

After Marnie's treatment was completed in 2005, the Kaufmans set up the Adenoid Cystic Carcinoma Research Foundation to try to speed up the development of therapies for the disease. They raised \$2 million and formed a scientific advisory board. But they quickly realized that Jeffrey needed to serve as the project manager. "Everyone else had so many other obligations," he said. The only way to push faster was if patients and their advocates drove and coordinated the work.

Jeffrey told me that as he plunged into studying ACC, he came to understand that although every rare cancer is at a different stage in the research process, overall they share similar problems. There is usually a lack of information about the disease, a lack of model systems for testing leads, and a lack of effective therapies. He also recognized at the outset that, to make progress, most researchers of rare cancers need the same building blocks: access to specimens that can then lead to the creation of cell lines; genomic and proteomic studies to look for compound leads; and xenograft models for screening potential agents.

In the case of ACC, the Kaufmans helped organize and increase the number of fresh tumor samples that got banked. They met with patients, surgeons, and pathologists to help coordinate tissue banking when patients underwent surgery. Using money they raised, they set up a biobank and got a group of academic centers that each saw a number of ACC patients to agree to bank tumors in a standardized way, share specimens, and pool their research. Instead of waiting for proposals to come in for the scientific advisory board to evaluate, using the research plan that the board created, the Kaufmans went out and contracted with researchers, companies, or organizations to provide the services they needed. In this way, they were able to quickly get

tumors profiled. Approximately a dozen xenograft models were established, and combinations of existing drugs are now being tested against the models in a search for new therapies. Moreover, the price tag for all of this was less than they expected. The Kaufmans were able to take advantage of economies of scale, approaching scientists who were already doing studies, welcomed the chance to study a rare, hard-to-get cell line like ACC, and therefore agreed to add the tumor to their existing work. Now Jeffrey would like to expand this model to tackle other rare cancers. With some seed funding, he believes that the research team he set up to drive therapies for ACC could do something similar for five to 10 other rare tumors over the course of the next few years.

There is now a cadre of patient advocates like Jeffrey Kaufman who are able to drive this kind of work. What is needed is the development of a system to support and accelerate it. We need a novel partnership between patients, the government, and academic cancer centers like the ones where Curiel and Gelbard work to focus on rare cancers. Each group plays a critical role. The National Cancer Institute needs to bring its moral authority and some strategically placed seed money to the table to convince the academic centers that see the majority of patients with rare cancers to form a rare cancer network. These centers must agree to establish a biobank for rare tumors and share any specimens that are collected. Patient-driven groups like the Adenoid Cystic Carcinoma Foundation, the Multiple Myeloma Research Consortium, and the Genetic Alliance have all created successful biobanks and have indicated that they are willing to share what they learned. There is no need to spend years debating protocol; members of the network should meet, choose one of the existing models as a template, and get started immediately.

In Jeffrey Kaufman's proposal, one of the criteria for determining which rare cancers get addressed first is the existence of active patient advocacy. This emphasis is novel and important. Patient groups who raise funds, set up scientific advisory boards, and demonstrate effective project management skills should be eligible for some form of assistance from the National Cancer Institute, whether it is in the arena of strategic advice, small amounts of matching funds to what patient groups can raise on their own, or identification and entry into existing National Institutes of Health projects that can be expanded to include a particular rare cancer. But the notion that the patient or the patient advocate will need to be the project driver is the key here; without the patient, the sense of urgency gets lost amid all the other competing claims that physicians and scientists face.

The war on cancer cannot be a war only on behalf of certain patients or certain tumors. Our goal should be, at a minimum, a basic knowledge about all cancers—only then will we be able to see the interconnections and make faster progress for everyone. We need to create an information infrastructure that will allow patients, not only researchers, to contribute potential leads for new drugs. Sometimes through their deep immersion, they are able to see connections that have eluded scientists.

Some might look at the story of Andy and argue that it is an unproven model and that turning to patients to drive efforts into finding cures for cancer is risky and unconventional. There is no doubt that SNUC remains as lethal as it was 5 years ago, when Andy and I first met. There is still no cure for ACC, multiple myeloma, or many other rare cancers where patient-driven drug searches are underway. But that would ignore the advances that have been made in just a few years thanks to these efforts, including new biobanks, cell lines, animal

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models, and drugs that extend patients' lives, all in rare cancers that otherwise would likely have gone unstudied. The standard approach has not been working for patients with rare cancers; it is time to try something different. Curiel's words to Andy years ago still resonate for patients today: given that we cannot cure them, we owe them a chance to take charge and find a better way.

Editor's Note

Although this Perspective is published as a freestanding contribution, we felt that it would be appropriate to underscore the difficul-

ties in performing research in uncommon tumors by publishing it with two original reports on small-cell carcinoma of the bladder and adenocarcinomas of the small bowel.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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